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OF METHYMYCIN

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THE UNIVERSITY OF ALBERTA

TOWARDS THE SYNTHESIS OF METHYMYCIN

by

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A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE
OF
DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA
SPRING, 1973

TO

MY PARENTS

AND TO

RICK RADISSON, C. B.

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled

"TOWARDS THE SYNTHESIS OF METHYMYCIN"

submitted by KENNETH EDWARD WILSON in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

The macrolide antibiotics that possess complex substitution patterns in the medium and large lactonic rings constitute a particularly interesting class of natural products, several members of which have important medicinal applications. The underlying factors that give rise to the common stereochemical features exhibited by these macrolides have yet to be determined. To date, no complex macrolide has been synthesized.

A synthesis of the lactone portion (methynolide, 25) of the macrolide methymycin (1) has been initiated. Our approach involves the construction of the right-hand (C_1 to C_7) and left-hand (C_8 to C_{13}) halves of methynolide as suitably substituted aliphatic chains. The joining of the two halves, followed by cyclization, completes the scheme.

This thesis reports the successful, efficient synthesis of the lactonic acid (±)-32, which contains all stereochemical features present in the right-hand portion of methynolide. A method has also been developed to construct the left side of methynolide. Initial model experiments for the condensation of the two halves have provided encouraging results. Two possible procedures to carry out the final cyclization are also discussed.

In the course of this work it became desirable to effect an intramolecular epoxidation. The practicality of such a reaction is briefly examined.

It is the ultimate goal of our laboratory to develop a general synthetic scheme for the macrolide antibiotics, based on a stepwise elongation of a branched aliphatic chain, introducing new side groups with the desired relative stereochemistry. Such a synthesis not only should greatly assist research concerning this family of antibiotics but also should be of importance, in a more general sense, to the synthetic investigations of other naturally occurring substances.

ACKNOWLEDGEMENTS

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CHAPTER 1

THE STRUCTURE OF THE MACROLIDE ANTIBIOTIC METHYMYCIN

Introduction to the Macrolide Antibiotics

In 1950 Brockmann and Henkel[1] reported the isolation of a new biologically active, basic compound from a Streptomyces microorganism. This substance, picromycin, represented the first recognized member of a heretofore unknown family of antibiotics. By 1956, Streptomyces had yielded other novel compounds (e.g. methymycin, erythromycin) whose chemical behaviour indicated a close kinship with picromycin. At this time, researchers had established the presence of a lactone linkage in methymycin,[2] picromycin,[3] and erythromycin,[4] incorporated in a medium- or large-ring system. Accordingly, Woodward[5] proposed the family name "macrolide" for these antibiotics.

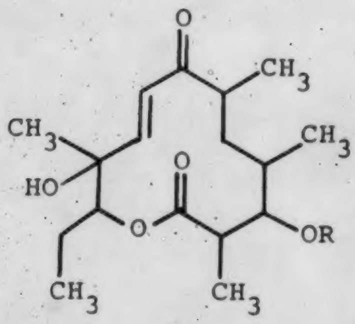
During the intervening years, so many lactonic natural products satisfying Woodward's original definition have been identified that the term "macrolide" has adopted recently a more restricted interpretation. The large-ring lactones containing a conjugated tetraenic (or longer) chromophore, such as amphotericin B (11), are referred to as polyene macrolides. The substances that have a strong structural resemblance to Brockmann's picromycin are called nonpolyene macrolides, or more simply just macrolides. All other compounds (e.g. the macrotetralide 12) are termed pseudomacrolides. Even with this classification, more than fifty representatives of the macrolide class are now known.

The macrolides are characterized by a highly functionalized twelve-, fourteen-, or sixteen-membered lactone. Oxygen-containing substituents are numerous and diversified. Furthermore, at least one deoxy sugar residue is found, linked by a glycosidic bond to the lactone. Usually an amino sugar is also present. Reference is made to several macrolides in this thesis. Their structures are represented collectively in Figure 1 along with one member of the polyene class and one pseudomacrolide. Definitive structures for the sugars are shown in Figure 2.

As antibiotics, all macrolides possess antibacterial activity. However only four members, erythromycin, oleandomycin, spiramycin, and carbomycin (magnamycin), are presently being used in chemotherapy.[6] Their advantage over the more widely used drugs lies in their low toxicity and the almost complete absence of side effects. The antibiotics are effective mainly against Gram-positive pathogens. The mode of action is primarily bacteriostatic, however at concentrations higher than the minimum inhibitory level definite bacteriocidal behaviour is observed.

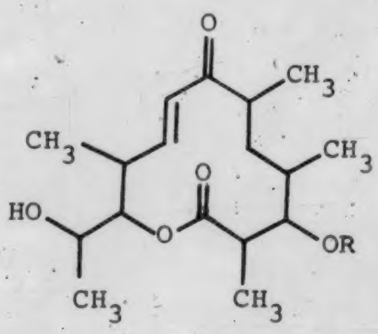
Figure 1: The Macrolide Lactones

(Nonpolyene) Macrolides



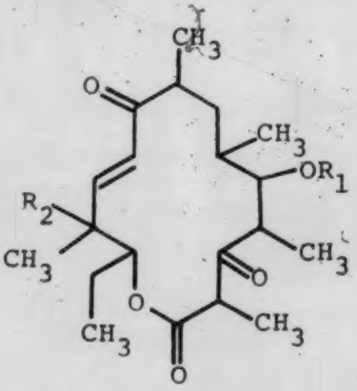
1

Methymycin (R=desosaminyl)



2

Neomethymycin (R=desosaminyl)

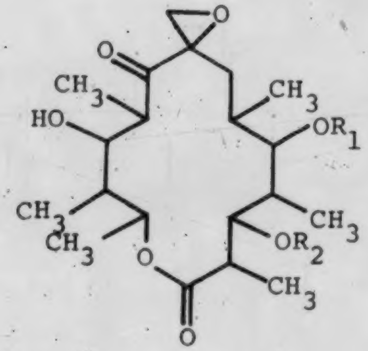


3: Narbomycin

(R_1=desosaminyl, R_2=H)

4: Picromycin

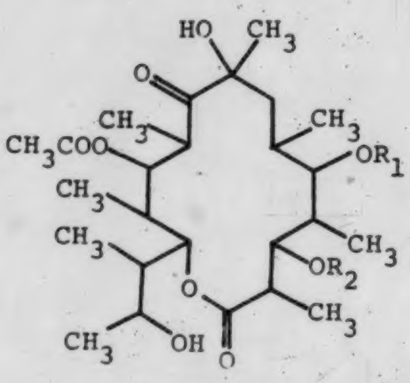
(R_1=desosaminyl, R_2=OH)



5: Oleandomycin

(R_1=desosaminyl,

R_2=oleandosyl)

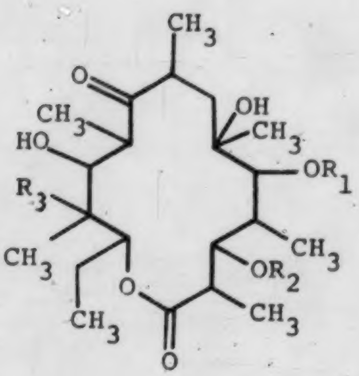


6: Lankamycin

(R_1=chalcosyl,

R_2=4-O-acetylarcanosyl)

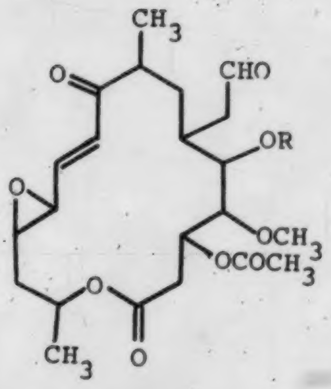
Figure 1 (continued)


CH3
O
CH3
HO
OH
CH3
OR1
R3
CH3
CH3
OR2
O
CH3
CH3
O

7: Erythromycin A
(R_1=desosaminyl,
R_2=cladinosyl, R_3=OH)

8: Erythromycin B
(R_1=desosaminyl,
R_2=cladinosyl, R_3=H)

9: Erythromycin C
(R_1=desosaminyl,
R_2=mycarosyl, R_3=OH)

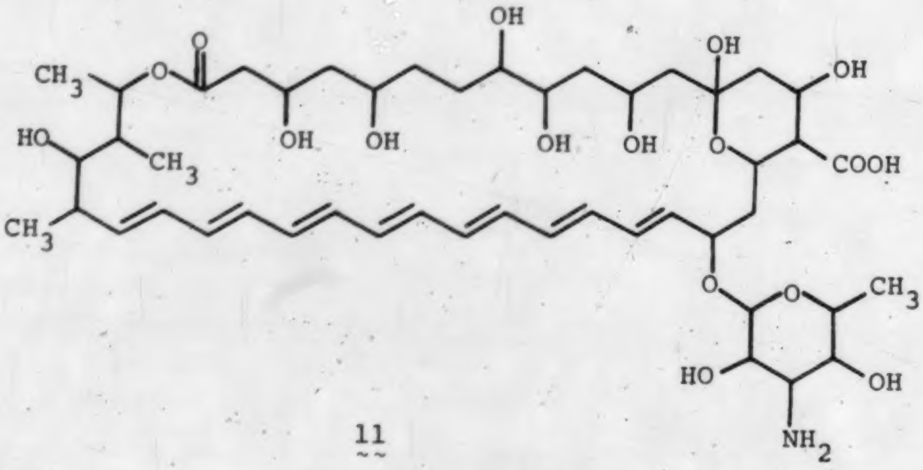

CH3
O
CHO
OR
O
OCH3
OCOCH3
O
CH3
O

10

Carbomycin A (Magnamycin A)

Figure 1 (continued)

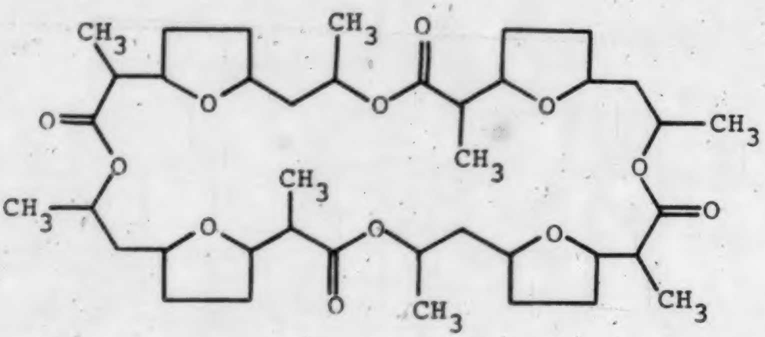
Polyene Macrolides



11

Amphotericin B

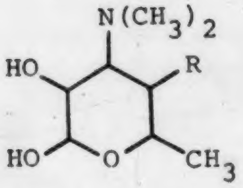
Pseudomacrolides



12

Nonactin

Figure 2: The Macrolide Sugars

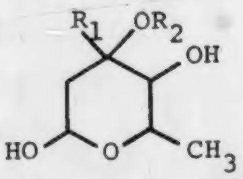

N(CH3)2
HO
R
HO
O
CH3

13: Desosamine*

(R=H)

14: Mycaminose

(R=OH)


R1
OR2
OH
HO
O
CH3

15: Oleandrose

(R_1=H, R_2=CH_3)

16: Cladinose**

(R_1=CH_3, R_2=CH_3)

17: Mycarose

(R_1=CH_3, R_2=H)

* Chalcose is derived by replacing the N,N-dimethyl amino group in desosamine with methoxyl.

** Arcanose is the C_4 epimer of cladinose.

Although methymycin exhibits roughly the same range of biological action as the drugs mentioned above, its inhibitory power is much less (ca. 10^2 to 10^3 fold). Consequently little interest has been shown in methymycin as a potentially useful drug. The macrolides have the common feature of inhibiting bacterial protein synthesis at the ribosomal level.[6] Controversy still exists concerning the exact step in the protein-synthesis mechanism that is disrupted. Influence that the antibiotics exert on other subcellular processes may also contribute to the macroscopic effects of the drugs. Little or no inhibition of bacterial RNA or DNA synthesis has been observed.

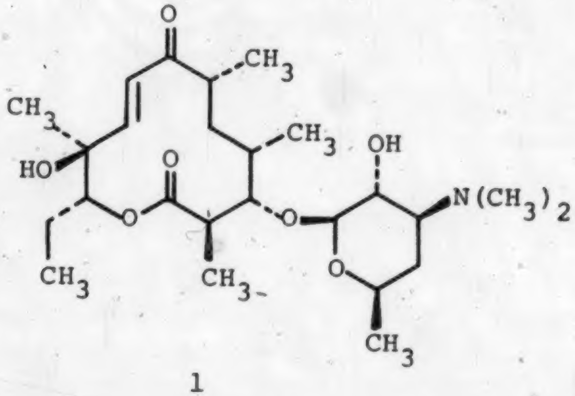
The macrolides have proved to be noble adversaries for the structural organic chemist. One of the common difficulties is the constitutional instability of the macrocyclic aglycone moiety under ordinary experimental conditions. Mildly basic conditions often lead to noncrystalline acyclic products arising from cleavage of the lactone. Macrolides containing β-hydroxy carbonyl groups (e.g. erythromycin A) may tend to suffer dehydration in both mildly acidic and basic media. Unfortunately, rather more complex alterations of the lactone skeleton often occur under acid conditions. The compounds resulting from these deep-seated changes can be intriguing and their structures may suggest certain conformational properties of the macrolide. Finally, the varied substitution pattern of oxygenated functions about the ring results in certain chemical procedures working for one macrolide but not for another. For instance, in order to simplify the problem of determining the constitution of a macrolide, it has been found desirable to free the aglycone portion of the sugar residue(s). The glycosidic bond of amino sugars such as desosamine (13) is abnormally stable. More stringent acid conditions must be used to effect cleavage. In the case of methymycin it is possible to remove desosamine and successfully hold the aglycone system intact. However with erythromycin A the mildest conditions that remove desosamine result in extensive degradation of the 14-membered ring.[7]

Once the constitutional nature of a macrolide has been established, definition of the absolute stereochemistry of asymmetric centres in the lactone presents a second major problem. The chemist must be able to obtain fragments of the ring in a way that there has been no chance for epimerization of the asymmetric carbons isolated in the fragments. *A priori*, one may indeed suspect that the configuration of the methyl group at C_2 in picromycin, which is straddled by two carbonyl functions, would demand great care to preserve. Of the aglycone ring carbons in erythromycin A, 85% are chiral. To identify rigorously the one correct stereoisomer from 1024 possible candidates becomes so overwhelming that to date, of the more than 25 constitutionally established non-polyene macrolides, only one, erythromycin A, has rigorously defined stereochemistry. This resulted from an X-ray analysis of its hydroiodide,[8] which is to date the only derivative of a non-polyene macrolide that has been obtained in a crystalline form suitable for single-crystal X-ray analysis. Recently Ganis, Avitabile, Mechlinski, and Schaffner reported the X-ray structure of the N-iodoacetyl derivative of the polyene antibiotic amphotericin B.[9]

The configurations of other macrolides have been proposed on the basis of strong chemical and spectroscopic evidence. The methods used have included: (1) the correlation of degradation products with substances of known absolute stereochemistry, (2) ORD, (3) molecular rotation differences, but most especially (4) nmr spectroscopy. Nmr analysis has proved so valuable primarily because of two facts. Firstly, the aglycone portion of several macrolides containing a 14-membered lactone have single conformations in solution, which are similar enough to one another to permit nmr correlations. Thus a comparison of the nmr spectrum of lankamycin (6) with those of the conformationally similar erythromycins has helped determine the structure of 6.[10] Secondly, the observed coupling constants between vicinal protons are either small (1-3 Hz) or large (9-11 Hz). As a result, conclusions may often be confidently drawn concerning the relative stereochemistry of vicinal substituents. It is well known that such factors as ring strain, the presence of polar groups, and the specific orientation of those polar groups may influence significantly the observed vicinal coupling constants. A macrolide with a highly substituted lactone would be expected to be strained, because of both the inherent distortion in the parent ring system itself and the mutual crowding of the ring substituents. Furthermore all macrolides possess polar groups. Therefore the interpretation of vicinal coupling constants in the range 4-8 Hz may be dangerous. Certainly if a conversion of coupling constants into dihedral angles is required in these intermediary cases, then critical studies of closely related systems must be included. Conformational assignments based on nmr, ORD, or molecular rotation differences cannot be considered as rigorously proved.

Constitution of Methymycin

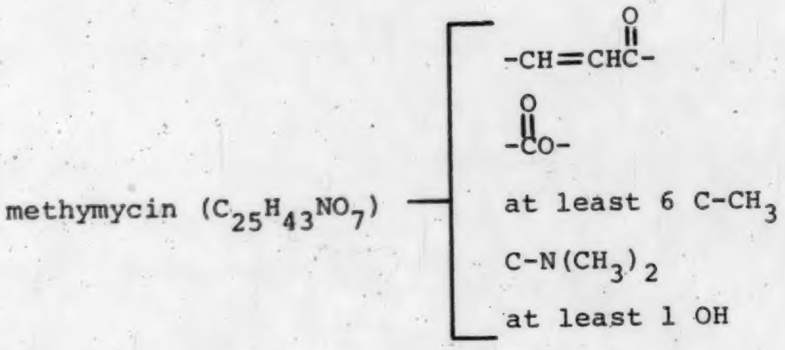
Methymycin (1) was the first macrolide to have its constitutional structure elucidated (1956). This pioneering work was carried out with efficiency by C. Djerassi and his colleagues.[2] However fourteen years elapsed before a completed picture (see below) of the antibiotic was proposed by Rickards et al.[11] Perhaps one



1

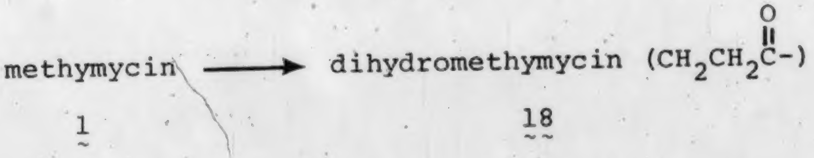
reason for the slow progress on methymycin's stereochemistry is that the antibiotic fell into disfavour with organic and biological chemists when it became apparent by 1960 that it had no chemotherapeutic worth. The structure and stereochemistry of the desosaminyl residue were determined by the standard methods of carbohydrate chemistry and will not be discussed in this chapter.

By 1953 a group of researchers at The Squibb Institute for Medical Research reported the isolation of a new crystalline metabolite, methymycin, from Streptomyces venezuelae.[12] This substance exhibited activity against certain Gram-positive bacteria. The same chemists characterized methymycin as a dextrorotatory base with an empirical formula $C_{25}H_{43}NO_7$. The uv spectrum indicated the presence of an α,β-unsaturated carbonyl chromophore. This was supported by ir absorptions ($CHCl_3$) at 1681 and 1628 cm^{-1}, and by polarographic studies. The ir spectrum also contained a strong hydroxyl band (3413 cm^{-1}) and a second carbonyl stretching band (1719 cm^{-1}) that was later ascribed by Djerassi and coworkers[13a] to an ester or a lactone. Standard degradative procedures showed the presence of at least six C-methyl groups and of a tertiary dimethylamine. This information is summarized below:



$$\text{methymycin } (C_{25}H_{43}NO_7) \left[\begin{array}{l} -CH{=}CH\overset{O}{\overset{\|}{C}}- \\ -\overset{O}{\overset{\|}{C}}O- \\ \text{at least 6 } C{-}CH_3 \\ C{-}N(CH_3)_2 \\ \text{at least 1 OH} \end{array} \right.$$

Two years later Djerassi _et al_.[2,13] extended the work of the Squibb group and successfully pieced together the facts into a total structure. Hydrogenation of methymycin over a palladium on charcoal catalyst in ethanol reduced the carbon-carbon double bond, giving dihydromethymycin (**18**). On the other hand, hydrogena-



$$\underset{\mathbf{1}}{\text{methymycin}} \longrightarrow \underset{\mathbf{18}}{\text{dihydromethymycin}}\ (CH_2CH_2\overset{\overset{O}{\|}}{C}-)$$

tion under more severe conditions led to two products, tetrahydromethymycin (**19**) in which the α,β-unsaturated carbonyl had been reduced to the corresponding saturated alcohol and a hydrogenolysis derivative, tetrahydrodesoxymethymycin (**20**), in which some oxygen other than the one of the unsaturated carbonyl had been lost. Dihydromethymycin (**18**) was reduced cleanly by sodium borohydride to

$$\mathbf{1} \longrightarrow \begin{array}{c} \text{tetrahydromethymycin}\ (CH_2CH_2CHOH) \\ \mathbf{19} \\ + \\ \text{tetrahydrodesoxymethymycin}\ (-O,\ CH_2CH_2CHOH) \\ \mathbf{20} \end{array}$$

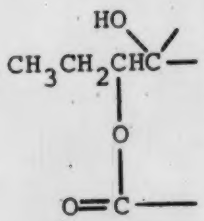
19 which reacted with perbenzoic acid to form only the corresponding N-oxide. All elements of unsaturation in **1** had therefore been accounted for. As a result methymycin contained two rings.

Two acetylable hydroxyl groups were part of **1**. Neither could be oxidized to a ketone.

1 → methymycin diacetate

21

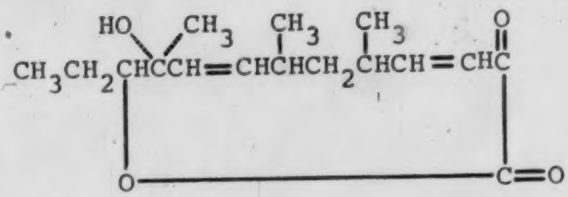
Methymycin was inert to periodic acid. However by first reducing the antibiotic with lithium aluminum hydride and then adding one equivalent of periodic acid, a good yield of propanal was obtained. Thus methymycin contained a masked glycol in which one of the hydroxyls was protected as the ester or lactone. On this evidence, the structural fragment **22** was then considered part of methymycin. The free OH was assumed to be tertiary to account for its resistance to oxidation.



$$\mathrm{CH_3CH_2CH(O{-}C(=O){-})C(OH)(-){-}}$$

22

By this stage in the investigation, it was evident to Djerassi that the chemical properties of methymycin strongly resembled those reported for the antibiotics, erythromycin (**7**, **8**, and **9**) and picromycin (**4**). Both latter compounds were known to contain a lactone linked by a glycosidic bond to a basic sugar, desosamine (**13**).[3,4] In addition, picromycin was thought* to have the chemical composition $C_{25}H_{43}NO_7$, identical to that of methymycin. In fact Brockmann and Oster[3] had advanced a working model (**23**) for the degradation product cromycin (= picromycin - desosamine). The American workers had accounted for five



23

of the seven oxygens in **1**. They reasoned that if methymycin did belong to this group of lactonic antibiotics, then the remaining two oxygens might be present as an acetal. This was so. Careful hydrolysis of **1** in aqueous sulphuric acid provided the desosamine salt as well as a 20% yield of the freed aglycone fragment, methynolide (**25**, $C_{17}H_{28}O_5$). Little doubt remained that methymycin was a

---

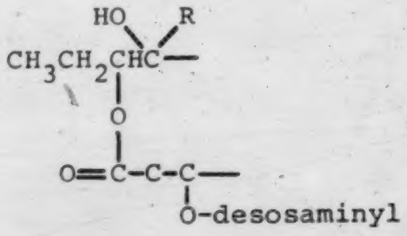
*Not until 1968 was the molecular formula of picromycin corrected to $C_{28}H_{47}NO_8$.[14,15]

$$\mathbf{1} \longrightarrow \underset{\mathbf{25}}{\text{methynolide}} + \underset{\mathbf{13}}{\text{desosamine}}$$

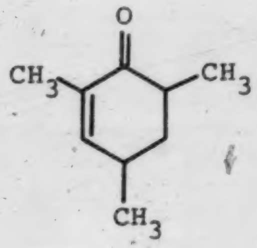
lactonic antibiotic.

The newly liberated hydroxyl in **25** was oxidized to a ketone. When the product, dehydromethynolide (**26**), was treated with aqueous base and then acidified, 0.6 mole equivalent of carbon dioxide was evolved. The result places the desosaminyl residue on the carbon β to the lactone carbonyl. The partial structure of **1** was elaborated to **27**. The results of two more reactions gave the information necessary to complete the picture.

The first key was the degradation of methymycin by alkali fusion (KOH, 360°) to 2,4,6-trimethyl-2-cyclohexenone (**28**). On the assumption that **28** likely arose

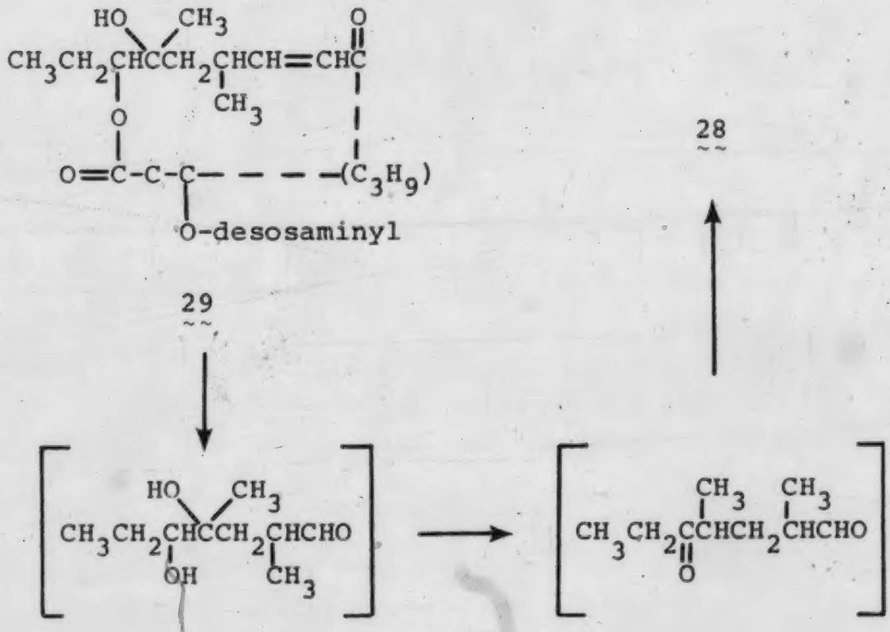


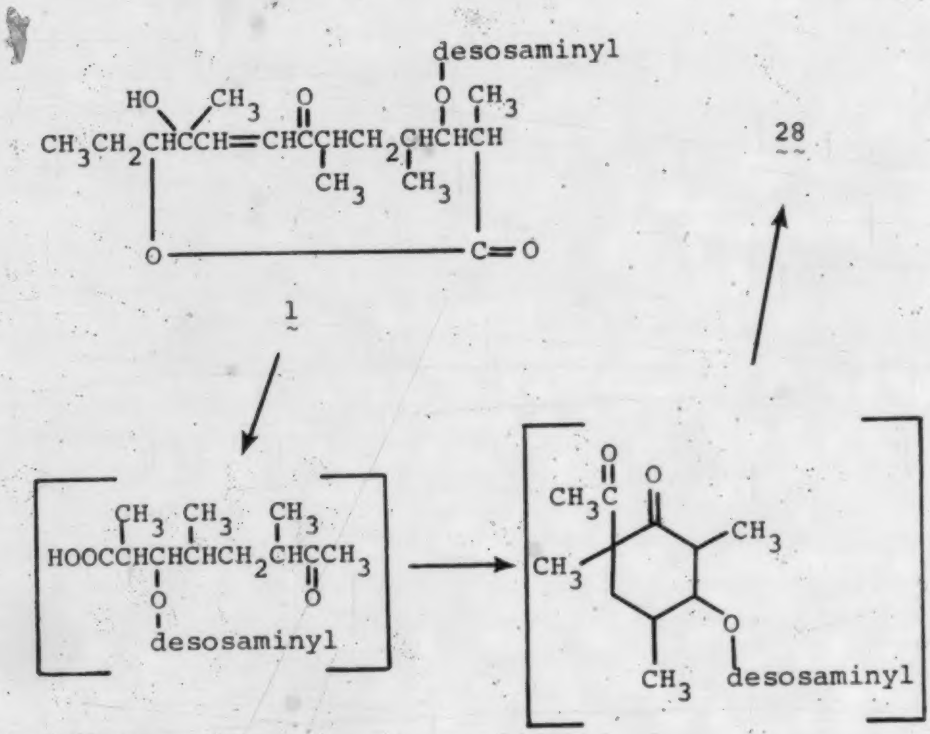
27



28

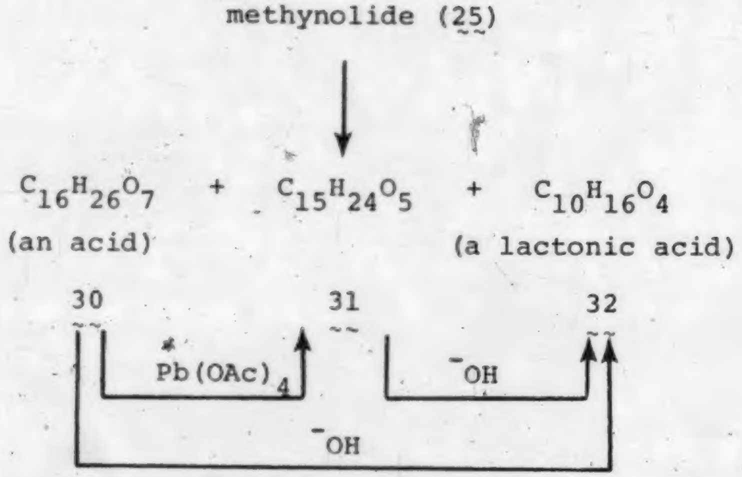
from an aldol condensation or a Claisen-type condensation of an appropriate aglycone fragment, two possible ways (29 and 1) to extend partial structure 27 were suggested. The second method led to a potential total structure for methymycin.

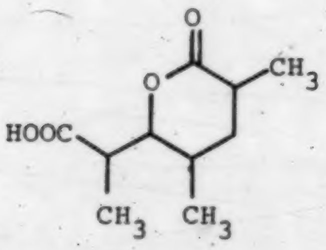

HO CH3
CH3CH2CHCCH2CHCH=CHC
O
CH3
O
O=C-C-C- - - -(C3H9)
O-desosaminyl
29
28
HO CH3
CH3CH2CHCCH2CHCHO
OH CH3
CH3 CH3
CH3CH2CCHCH2CHCHO
O



Mild permanganate oxidation of methynolide (25) provided the final evidence required to firmly fix the structure of methymycin as indeed 1. Excellent experimental work resulted in the isolation of three crystalline substances, 30, 31, and 32. Characterization of the products revealed the following interrelationships.

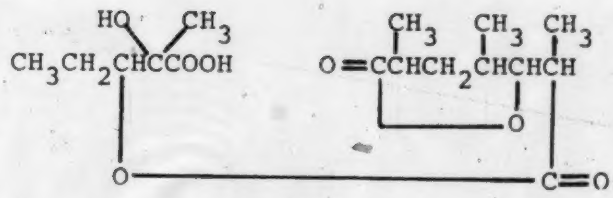
The smallest fragment (32) was identical to a lactonic acid isolated earlier from picromycin and narbomycin by V. Prelog *et al.*[16] These workers had identified 32 as the δ-lactone of 3-hydroxy-2,4,6-trimethylheptanedioic acid. These findings were completely in accord with


methynolide (25)
$C_{16}H_{26}O_7$
+
$C_{15}H_{24}O_5$
+
$C_{10}H_{16}O_4$
(an acid)
(a lactonic acid)
30
31
32
$Pb(OAc)_4$
^-OH
^-OH


O
O
CH3
HOOC
CH3
CH3

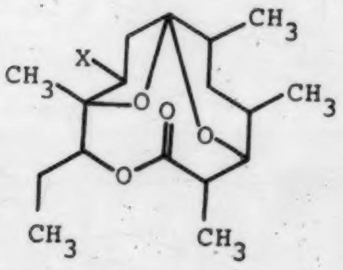
32

structure **1**. Furthermore, the interconversions and properties of **30**-**32** were so demanding that methymycin had to be **1**. From the structural assignment for **30**, the origin of **31** and **32** becomes apparent.


HO
CH3
CH3CH2CHCCOOH
CH3 CH3 CH3
O=CCHCH2CHCHCH
O
O
C=O

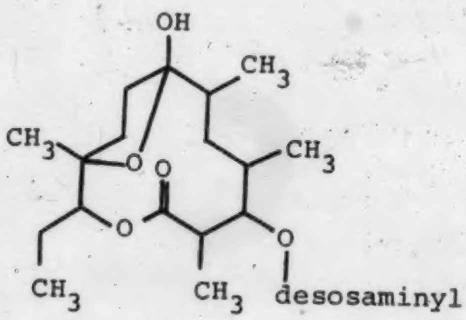
30

Before discussing the stereochemistry of the antibiotic, an interesting aspect of methymycin's chemistry should be mentioned. Djerassi had observed during the initial attempts to isolate methynolide by acid hydrolysis, that the use of aqueous hydrochloric acid or of methanolic sulphuric acid led to products which showed no evidence of an α,β-unsaturated ketone chromophore. With the structure of methymycin established, Djerassi was able to present strong evidence that these undesired substances were the spiroketals 33a,b.


X
CH3
CH3
CH3
O
O
O
O
CH3
CH3

33a: X=Cl

33b: X=OCH_3

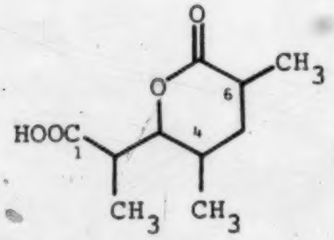

OH
CH3
CH3
CH3
O
O
O
O
CH3
CH3
desosaminyl

18

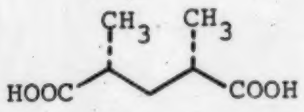
Apparently the aglycone fragment is stable as long as it retains the double bond. However once the double bond has been removed, the additional flexibility in the new system makes the carbonyl exceptionally prone towards attack by the hydroxyl groups on C_3 and C_{10}. In fact results suggest that dihydromethymycin (18) exists largely as the hemiketal.[2]

Absolute Stereochemistry of Methymycin

It was stated in the preceding section that Prelog has isolated the same (+)-lactonic acid (32) from permanganate oxidation of picromycin and narbomycin as Djerassi has from methynolide. The degradation studies[16] that established structure 32 also defined the relative stereochemistry of the C_4- and C_6-methyl groups as cis.



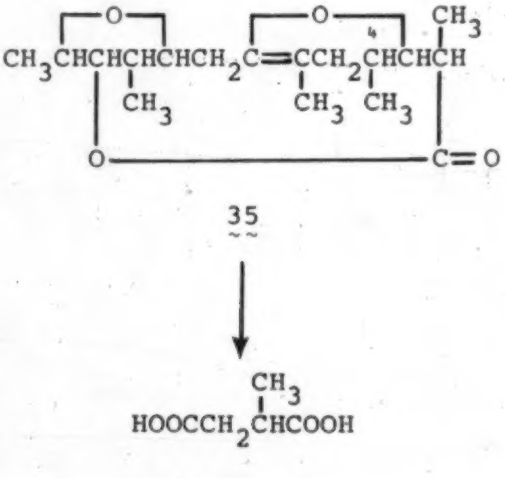
(+)-32



34

Pyrolysis of the lactonic acid and subsequent ozonolysis gave meso-α,α'-dimethylglutaric acid (34).

Two years later Djerassi and coworkers[17a] reported the structure of neomethymycin (2), an isomer of methymycin. The stereochemistry of carbons 2, 3, 4, and 6 of neomethymycin and methymycin had to be the same since the aglycone of the former was also oxidatively broken down to (+)-32. Under certain conditions, acid hydrolysis converted neomethymycin to 35 in high yield.[17b,c] From 35,

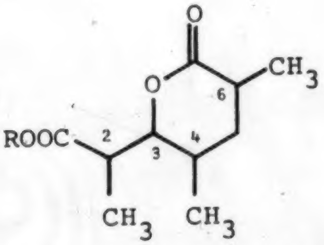

35

(-)-*S*-36

C_4 was successfully isolated as (-)-*S*-α-methylsuccinic acid (36). Consequently C_4 of methymycin had the *S* configuration and it followed that C_6 had *R*.

In 1963 Bergel'son and Batrakov[18a] claimed a synthesis for the racemate of the Djerassi-Prelog lactonic acid (+)-32. Later, based on evidence from an nmr study and from degradative work on this synthetic lactone, they concluded[18b] that the stereochemistry at C_2 and C_3 of methymycin is *S* and *R* respectively. These results were opposite to the prediction made earlier by Celmer on the basis of his "model" for macrolide stereochemistry. (Both Celmer's and the Russians' work are discussed in greater detail in later chapters.)

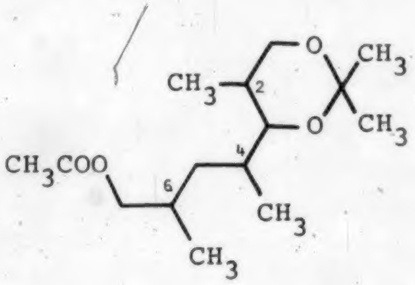
Because of the unexpected configurational assignments at C_2 and C_3 and because the identity of the Djerassi-Prelog (+)-lactonic acid with the synthetic racemate had been based solely on solution ir spectra, Rickards and Smith[11] in 1970 reinvestigated the problem. They also used nmr analysis extensively but the subject of their study was authentic natural lactonic acid (+)-**32**. The



(+)-**32**: R=H

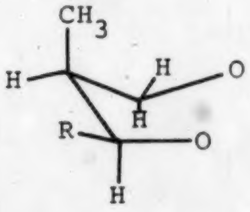
37: R=CH_3

vicinal coupling constant $J_{3,4}$ in both the lactonic acid and its methyl ester was 10.0 Hz. The authors concluded that H_3 and H_4 are anti-periplanar and the S configuration was ascribed to C_3. To gain insight into the orientation of the C_2-CH_3 group, **37** was converted by lithium aluminum hydride reduction, ketalization, and acetylation into **38**, a compound in which C_2 has become incorporated into a 1,3-dioxolane ring. For clarity, the numbered carbons of the lactonic acid have been transposed into 38. Relevant nmr vicinal coupling constants were: $J_{1a,2}$=1.5 Hz, $J_{1b,2}$= 2.3 Hz and $J_{2,3}$=2.3 Hz. As all three values are small,

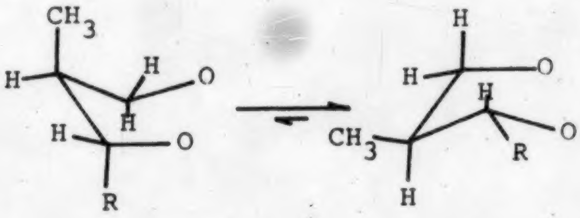


38

the authors stated that H_2 was syn-clinal to both C_1 protons and to H_3. Of the two structural orientations, 38-A and 38-B, consistent with the above, the latter was eliminated as conformationally unrealistic. The stereochem-



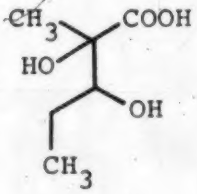
38-A



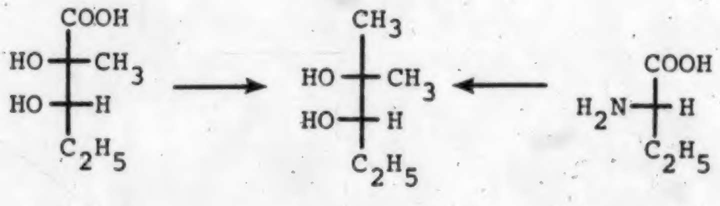
38-B 38-C

istry of C_2 is therefore R. Rickards and Smith further mentioned that the observed chemical shifts and coupling constants for 38 are very similar to those reported for other substituted 1,3-dioxolanes.[11a] Bergel'son and Batrakov apparently erred in concluding that their synthetic lactonic acid was the racemate of (+)-32.

Only the stereochemistry of the double bond, C_{10}, and C_{11} in methymycin remained undetermined. The nmr spectrum of methymycin established the double bond as *trans* while ozonolysis of the antibiotic led to the isolation of C_{10} and C_{11} as (+)-2,3-dihydroxy-2-methylpentanoic acid (39).[11b] Compound (+)-39 was identified as the *erythro* isomer when it was compared to authentic (±)-*erythro*-39. Final definition of the chirality at C_{10} and C_{11} as *S* and *R* respectively was possible when (-)-*erythro*-39 was correlated through 41 with (+)-*S*-butyrine (40). The struc-



(+)-39



(-)-39 41 40

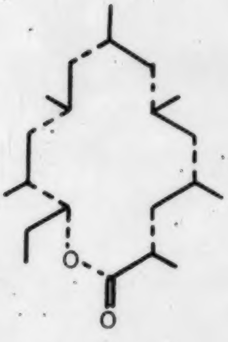
tures shown are in Fischer projection.

CHAPTER 2

A MODEL FOR MACROLIDE STEREOCHEMISTRY

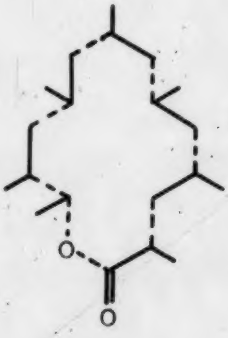
Introduction

By the early 1960's it had become increasingly apparent to several teams of researchers that among the macrolides that had been constitutionally defined, there were intriguing similarities. The lactone rings of the erythromycins A,[7] B,[19] and C,[20] oleandomycin,[21] narbomycin,[22] and the 12-macrolides, methymycin[2] and neomethymycin,[17a,b] all follow perfectly a biogenetic scheme involving a poly-β-ketone precursor, built up predominantly or exclusively from three-carbon subunits. The lactone carbon skeletons of the above macrolides are schematically shown below. Emphasis is placed on the subunit



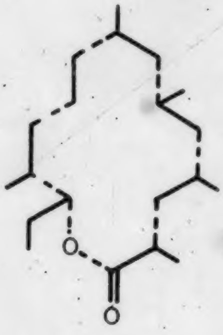
42

erythromycins A, B, and C



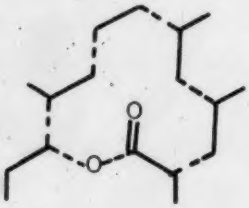
43

oleandomycin



44

narbomycin



45

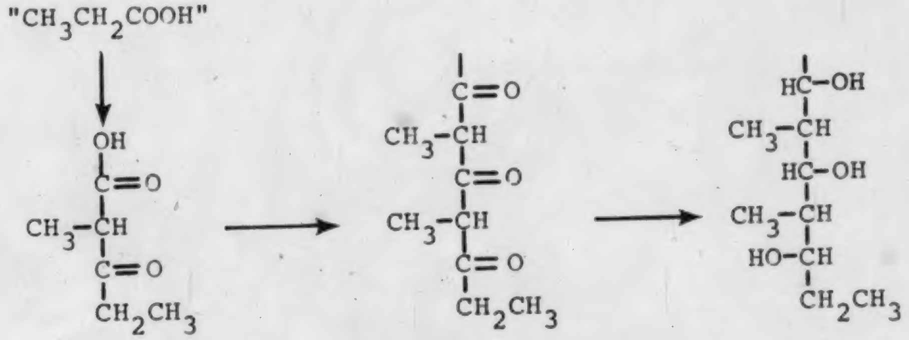
methymycin, neomethymycin

make-up. Furthermore each of these antibiotics contains the amino sugar, D-desosamine. The β-configuration at the anomeric centre had been established in erythromycins A[23,24] and B[23,25] and in oleandomycin.[23,25,26] The lactone of erythromycins A and B and of oleandomycin are also linked by a glycosidic bond to a neutral 2,6-deoxy sugar with the α-L-configuration.[23,25,26] Finally, close stereochemical relationships among macrolides have been convincingly demonstrated by the isolation of the Djerassi-Prelog lactonic acid (+)-**32** from methymycin, neomethymycin, picromycin, and narbomycin (see Chapter 1).

The combined weight of the above observations led W. D. Celmer to suggest in 1964 that one should be able to decipher a common pattern of stereochemistry that would be obeyed by all macrolides.[25] During the following two years Celmer pieced together a model that was to eventually verify his daring prediction.

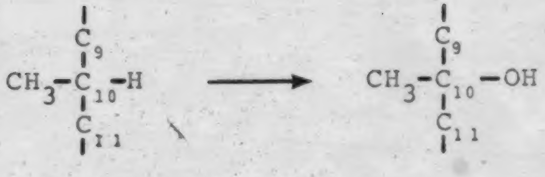
The Model

Many macrolides contain oxygen functions at unexpected sites on the aglycone ring, that is, sites that do not correspond to carbonyl locations in the poly-β-ketone. These special, "extra"[5] oxygens are thought to originate from oxidations at a late stage in the scheme for macrolide biosynthesis (see Chapter 3). During the construction of his model, Celmer was concerned with the configurations of alkyl substituents and with the configurations of asymmetric centres that bear oxygen functions derived from the carbonyl groups of the poly-β-ketone (47).



46 47 48

At the initiation of his work,[25] Celmer appreciated the significance of previous evidence revealing that bio-oxidations take place with retention of configuration. This inferred that any orientation of a methyl group at a chiral, lactonic carbon, predicted by a stereochemical model, should remain unaffected when a hydroxyl group (an extra oxygen) is introduced at that centre late in the macrolide biosynthesis. For instance, Celmer's model was to predict the configuration of C_{10} in the 12-macrolides as shown below in Fischer projection (49). Oxidation at C_{10} during the biosynthesis of methymycin should leave the orientation of the C_{10}-methyl unaltered. In 50, C_{10} has the *S* configuration which is in agreement

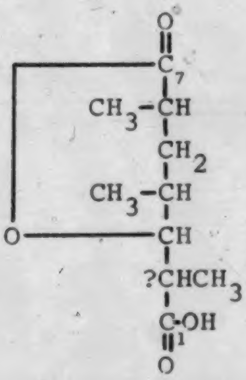


49 **50**

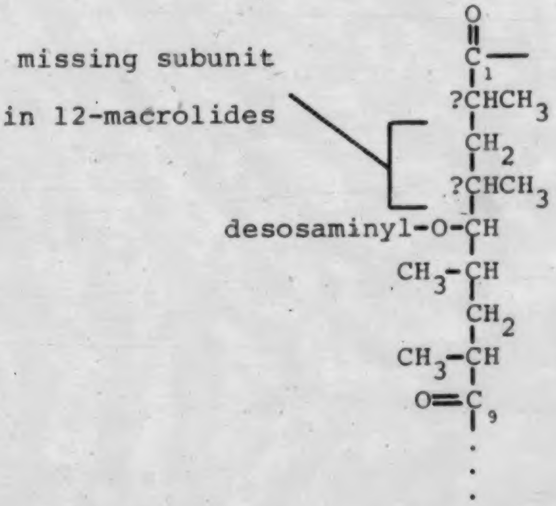
with experimental results.[11b]

Several points concerning macrolide stereochemistry were known in 1964 when Celmer started this work. Firstly, the four asymmetric centres in the Djerassi-Prelog lactonic acid (+)-**32** corresponded to C_2, C_3, C_4, and C_6 in methymycin and neomethymycin, and to C_4, C_5, C_6, and C_8 in narbomycin. Celmer proposed that the chiral centres of the first two 12-macrolides could be brought into line with the corresponding carbons in the 14-macrolide by assuming that the penultimate three-carbon unit had been skipped during the biosynthesis of the twelve-membered ring (see **51**).[23,25] Furthermore the chiral centres at C_4 and C_6 in (+)-**32** had been unequivocally assigned *R* and *S* respectively.[17c,d] Applying Hudson's Lactone Rule to (+)-**32** (below in Fischer projection), Celmer tentatively designated it as a D-lactone, thereby assigning an *S*-C_3 configuration.[23] A rudimentary model could then be written in Fischer projection as **51**.

Secondly, stereochemical work on several centres in erythromycin A had been reported in 1956 by Gerzon et al.[28] Their studies had been concentrated on the aglycone derivative, dihydroerythronolide A (52), in which the ketone at C_9 had been reduced. The "starred" carbons in 52 are the centres at which Gerzon suggested absolute

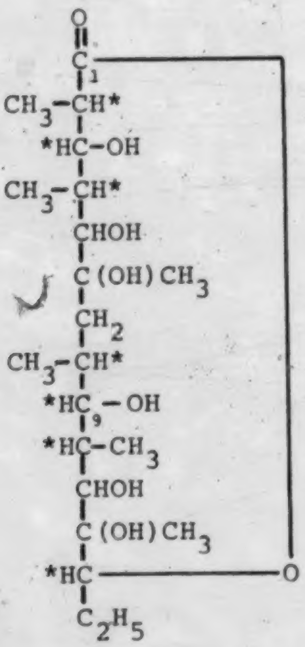

O
C_7
CH_3-CH
CH_2
CH_3-CH
O
CH
?$CHCH_3$
C-OH
1
O

(+)-32

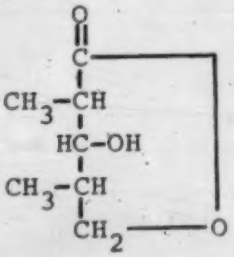

missing subunit
in 12-macrolides
O
C
1
?$CHCH_3$
CH_2
?$CHCH_3$
desosaminyl-O-CH
CH_3-CH
CH_2
CH_3-CH
O=C
9

51

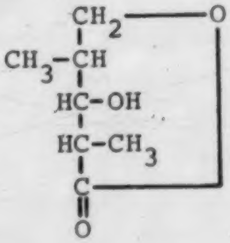
stereochemistry. The chiral carbons 2, 3, and 4 were isolated in the optically active lactone 53a. Reduction of 53a produced an optically inactive triol 53b, thus establishing the relative stereochemistry of the two methyl groups as meso. The trans relationship of the C_3-hydroxyl and the methyls was favoured since 53a had proven surprisingly resistant to β-elimination. A second lactone (54a), which contained C_8, C_9, and C_{10}, was also isolated from the degradation of **52**. The triol **54b** derived from **54a** still possessed optical activity. The two methyl groups in **54a** had to be *trans*. Finally, interpretation of the optical rotation values of **53a** and **54a** and of their hydrazides (**53c**, **54c**) led Gerzon to propose the configurations of **53a** and **54a**, shown above in Fischer projection. The configuration of C_{13} in **52** was defined also on the basis of optical rotation data.



52

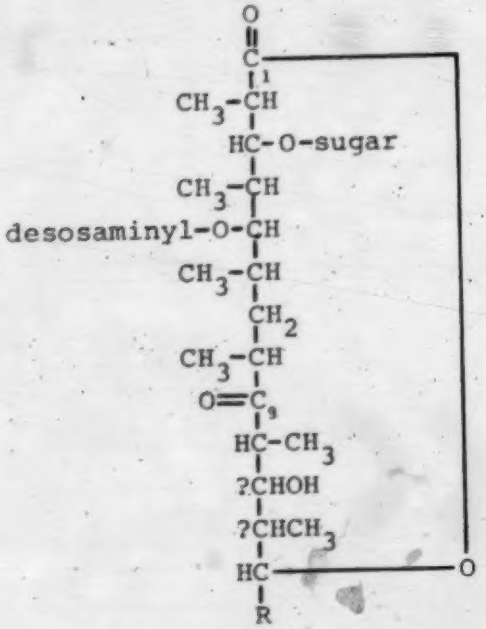


53a



54a

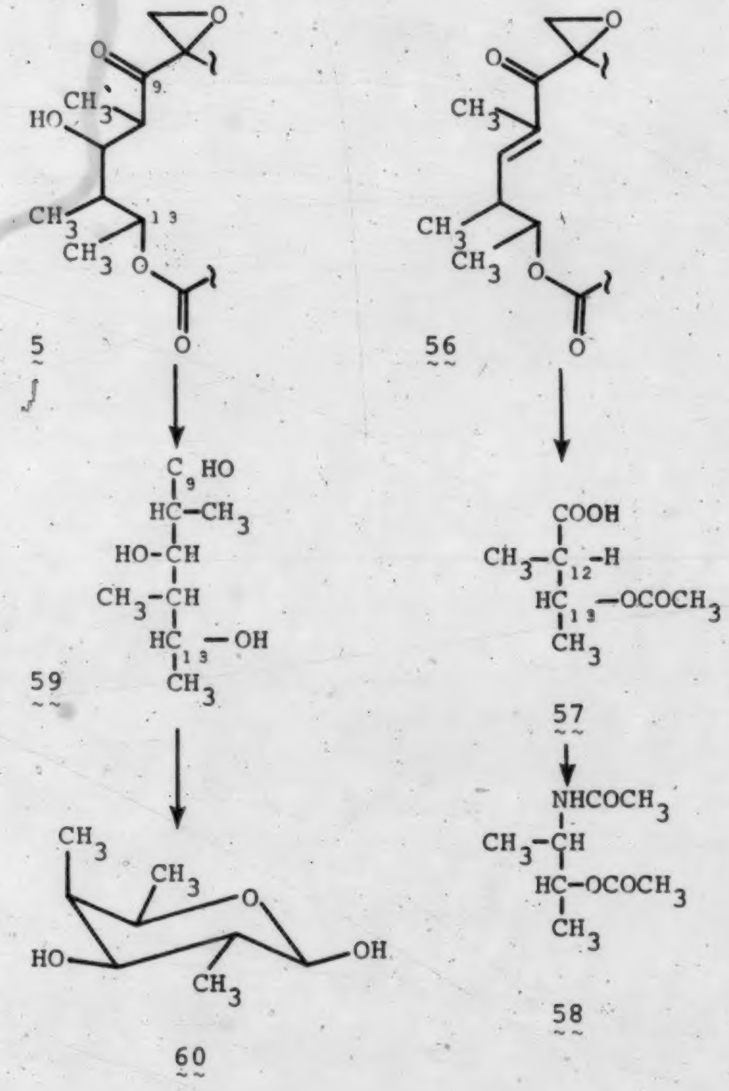
With Gerzon's results Celmer was able to elaborate the partial model **51** by now adding to it stereochemical designations at C_2, C_3, C_4, C_{10}, and C_{13} (see **55**). The configuration proposed by Gerzon at C_8 in **52** was consistent with Celmer's first partial model (**51**). Only chirality at C_{11} and C_{12} remained undefined, although many of the


O
C
1
CH3-CH
HC-O-sugar
CH3-CH
desosaminyl-O-CH
CH3-CH
CH2
CH3-CH
O=C
9
HC-CH3
?CHOH
?CHCH3
HC
O
R

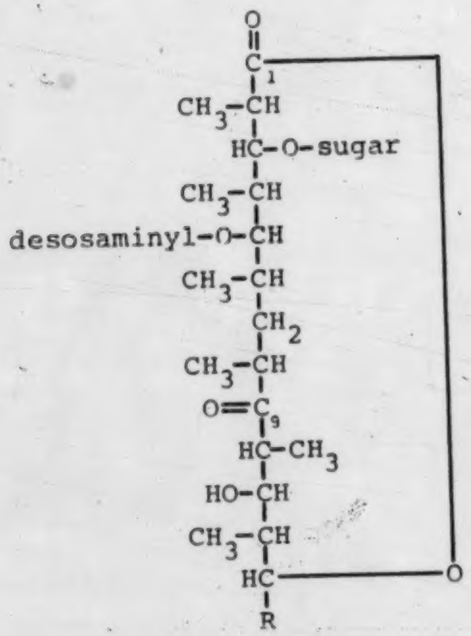
55

assignments in **55** required further support.

At the same time that he presented his model, Celmer[23,25] reported preliminary results concerning asymmetric centres in the 14-macrolide, oleandomycin (**5**), constitutionally elucidated in 1960.[21] Degradation of anhydrooleandomycin (**56**) yielded a 3-acetoxy-2-methylbutanoic acid (**57**) that contained C_{12} and C_{13}. A Curtius rearrangement transformed **57** into the known compound, (2S:3R)-2-acetamido-3-acetoxybutane (**58**). Moreover, by starting

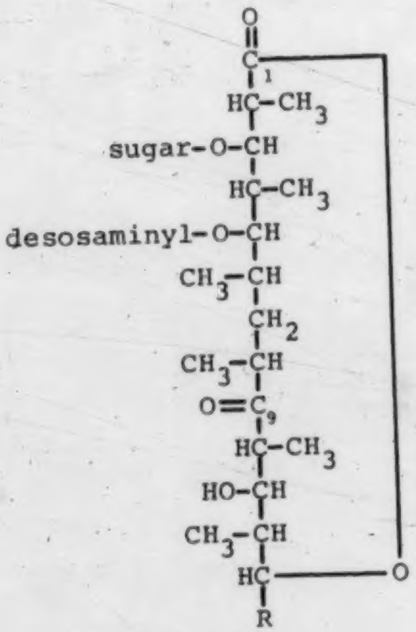

9
13
5
56
C 9 HO
HC–CH3
HO-CH
CH3-CH
HC 13 –OH
CH3
59
COOH
CH3–C 12 –H
HC 13 –OCOCH3
CH3
57
NHCOCH3
CH3-CH
HC-OCOCH3
CH3
58
CH3
CH3
O
HO
OH
CH3
60

with oleandomycin, C_{10}, C_{11}, C_{12}, and C_{13}, with their respective chirality preserved, could be isolated in a single compound, the synthetic sugar 60. The known configurations at C_{12} and C_{13}, nmr analysis, and ORD measurements firmly fixed the orientations at C_{10} and C_{11} as shown in 59 and 60. Celmer was now able to complete his model (61). The above experiments confirmed previous assignments to C_{10} and C_{13} in 55.



O
C
1
CH3-CH
HC-O-sugar
CH3-CH
desosaminyl-O-CH
CH3-CH
CH2
CH3-CH
O=C9
HC-CH3
HO-CH
CH3-CH
HC
O
R

61



O
C
1
HC-CH3
sugar-O-CH
HC-CH3
desosaminyl-O-CH
CH3-CH
CH2
CH3-CH
O=C9
HC-CH3
HO-CH
CH3-CH
HC
O
R

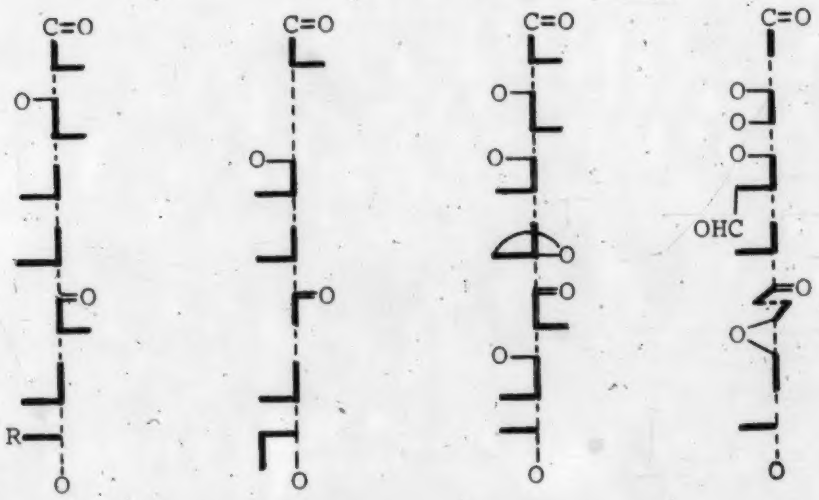
62

There was only one basic change that was subsequently made in 61. There appeared evidence[29] that Gerzon might have misinterpreted the optical rotation data of the lactones 53a and 54a and their hydrazides (53c, 54c). A reinvestigation of the problem led Celmer to conclude that the configurations of C_2, C_3, and C_4 must be reversed.[31,32] The revised model now stands as 62.

The key assumption made by Celmer in 1964 was that the 12-macrolides can be correlated to the 14-macrolides by theorizing that the penultimate three-carbon subunit has been skipped in the biosynthesis of the poly-β-ketone. The biosynthesis of the 16-macrolides (*e.g*. carbomycin A, 10) is known to differ from that of the smaller-ring antibiotics in one major feature. The poly-β-ketones are derived largely from two-carbon units. A consequence of this difference is that the sixteen-membered rings possess substantially fewer chiral centres. Nevertheless, where a three-carbon subunit has been incorporated into the poly-β-ketone, the stereochemistry of the methyl group is in accord with Celmer's model. Furthermore, the stereochemistry of the hydroxyl groups that originate from bioreduction of the carbonyls of two-carbon subunits is also predictable. Celmer made the correlation between 62 and the 16-macrolides by postulating the insertion of an extra two-carbon unit between the third and fourth subunits of 62. Figure 3 presents the model as schematic 63. Several macrolides are included to illustrate the congruence of the skeletal stereochemistry.

The model as presented below was confronted with at least six contradictions based on experimental work. In one case, mentioned earlier in Chapter 1, Bergel'son and Batrakov[18] published evidence that C_2 and C_3 in methymycin had respectively the S and R configurations. In 1970 Rickards and Smith[11a] brought C_2 and C_3 into accord by reversing the assignments. A second, more dramatic example concerns the chirality of C_8 in carbomycin A (10). In his classic paper[5] describing the constitution of carbo-

Figure 3: Stereochemical Correlation of Macrolide Lactones



63 model

64 methymycin

65 oleandomycin

66 carbomycin A

mycin A, Woodward reported the localization of C_8 in (-)-α-methylsuccinic acid. Consequently C_8 was ascribed the S configuration. Faced with a contradiction based on seemingly irrefutable experimental evidence, Celmer asked Professor Woodward to reexamine the α-methylsuccinic acid. The acid proved to be, in fact, the (+)-enantiomer.[33]

At present no macrolide has been shown to have stereochemical features that confront 63.

In conclusion, the model depicts: (1) the chirality at lactone centres bearing oxygen functions that are derived from bio-reduction of the carbonyl groups in the poly-β-ketone, (2) the chirality of alkyl substituents at lactone centres, (3) all carbohydrate components as 6-deoxypyranosides with identical chirality (either β-D or α-L) at the anomeric carbons, and (4) C_5 (or its equivalent) carrying a β-D-glycoside. The model makes no prediction of either the chirality at exocyclic centres (see neomethymycin and lankamycin) or the chirality of an extra oxygen attached at a ring carbon originally a methylene group of an acetate subunit in the poly-β-ketone (*e.g.* C_4 of carbomycin A, 66).

CHAPTER 3

BIOGENESIS OF MACROLIDES

Introduction

Whenever a particular family of naturally occurring substances is found to have important medicinal properties, there usually follows intense interest in unravelling the course of its biogenesis. Often even very rudimentary knowledge of the biosynthesis suggests changes in the nutrient composition of the medium on which the microorganism is grown, that may lead to greatly enhanced yields of the antibiotic. Such was the case with the macrolides. Not only had several members of this family important clinical applications, but also their structures were unique. Although some simple macrocyclic lactones, such as pentadecanolide,[34] had been isolated from plant sources, the known occurrence of large-ring compounds in nature was extremely limited. The macrolides had other outstanding properties. Antibiotics such as methymycin and erythromycin were highly substituted with methyl groups and with oxygen functions. In addition, rare sugars were often part of the structures.

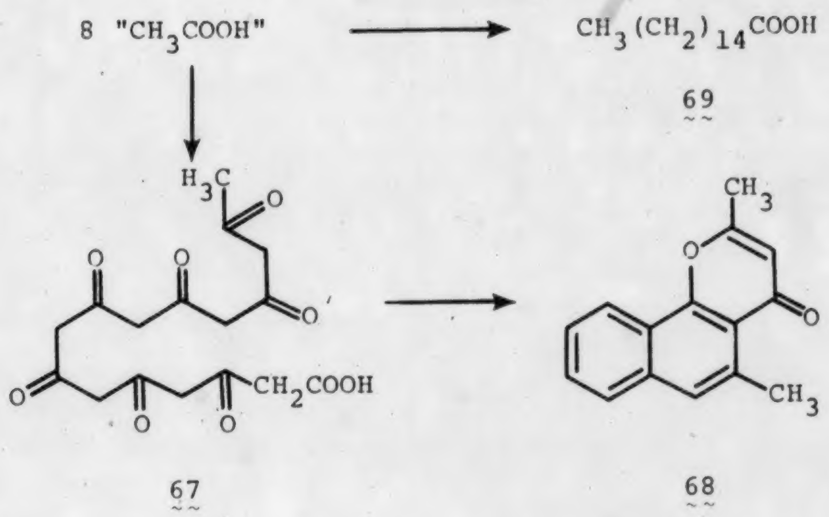
One of the first stages in a biogenesis study is the identification of the primary building units that combine to form the basic carbon skeleton. Often there are several units that are biologically equivalent (e.g. propionic acid, succinic acid, and methylmalonic acid), i.e. constitutionally different compounds, each of which can be envisaged to lead to the same natural product by a biologically realistic process. Moreover, the equivalent units may be reversibly interconvertible. As a result, experimental data must be interpreted cautiously. The advent of radioactive tracer techniques during the 1950's has greatly accelerated research into biosynthesis.

Later stages of investigation are concerned with the identification of discrete intermediates lying between the elementary building units and the final antibiotic. One technique employed is to block the biosynthetic process at various stages by chemically mutating the microorganism. The hope is then that the process will proceed normally up to the blocked step(s) but stop at that point, thus allowing intermediates to accumulate to concentrations that permit their isolation. The mutation process is often not very specific and the change induced in the microorganism might be such that "intermediates" isolated belong to a normally unimportant, secondary pathway. Even more confusing situations arise when the "intermediate" is in fact an abnormal metabolite that is reversibly connected to a true intermediate.

Several studies concerning the biosynthesis of methymycin have been reported but progress towards the understanding of how macrolides are formed has come primarily from studies of erythromycin production in S. erythreus. Because of this, most of the discussion to follow deals with the biosynthesis of the erythromycins. The origins of the lactone and the sugars are considered separately.

Biogenesis of Macrolide Lactones

The head-to-tail condensation of acetate units to form a poly-β-keto acid (e.g. 67) followed by subsequent cyclization and dehydration was a hypothesis first advanced in 1907 by J. N. Collie to explain the biosynthesis of aromatic natural products.[35] Much later, during the 1940's and early 1950's, it was indeed shown that acetate residues are the primary building blocks of not only aromatic compounds (e.g. eleutherinol, 68) but also of fatty acids (e.g. palmitic acid, 69). By analogy, K. Gerzon[36] and R. Robinson[37] suggested that similar compounds which appear to contain an extra methyl group might be formed by the incorporation of a propionate unit (or its biological equivalent) in the place of an acetate (the Propionate Rule). Later, with the elucidation of the carbon skeleton



(**42**) of the erythromycin lactone, Gerzon *et al.*[28] and Woodward[5] recognized that **42** follows perfectly the three-carbon regularity defined by the Propionate Rule.

Birch *et al.*[38] suggested an alternative scheme for macrolide biosynthesis, in which the basic carbon structure of the lactone is derived from acetate units. The methyl groups, originating from one-carbon donors, are then inserted at the activated methylene positions along the poly-β-keto chain.

The first evidence to show that the lactone portion (erythronolide) of erythromycin* is more closely

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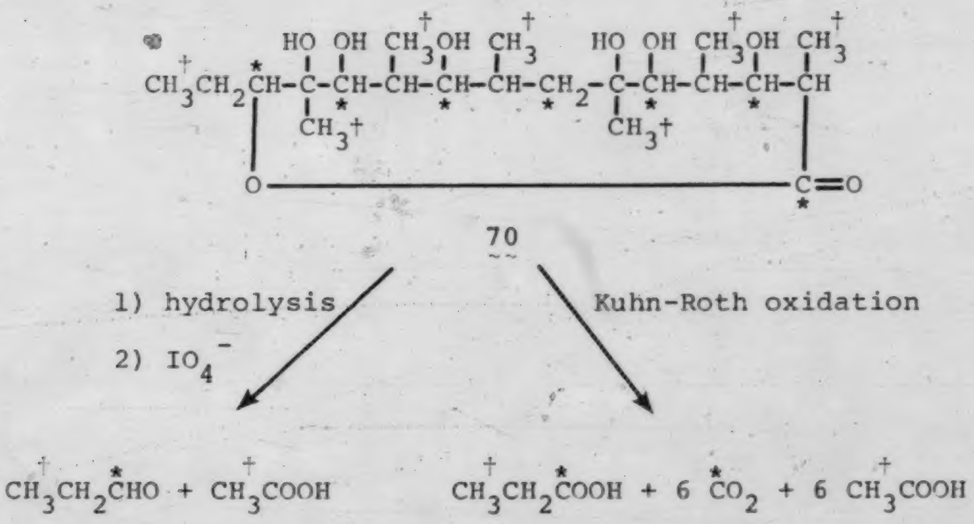
*In many of the papers dealing with the biogenesis of the erythromycins, it is not clear whether the authors have studied erythromycin A or in fact the mixture of the erythromycins (A, B, and C) obtained from *S. erythreus*.

related to propionate than to acetate was supplied by Vanek and coworkers in 1958.[39] They demonstrated that radioactive propionate was incorporated into erythromycin to a much greater extent than was labelled acetate. In both cases only the lactone contained radioactivity. The basic three-carbon substructure of erythronolide was confirmed later in numerous laboratories.

When S. erythreus was incubated in a medium containing propionic acid-1-^{14}C-3-^{3}H, Grisebach and coworkers[40] found that the isolated erythromycin had a ^{14}C:^{3}H ratio only 13-26% smaller than the ratio in the labelled propionic acid. If the three-carbon unit had first to be catabolized to acetate (or its equivalent) before use, then a more significant change in the ratio would have resulted. Degradation of the lactone derivative, dihydroerythronolide (70 depicts dihydroerythronolide A), outlined in Scheme 1, and examination of the radioactive products indicated that propionic acid had been incorporated efficiently with only minimal scrambling of the labels. In other words, propionic acid had been utilized as the intact, three-carbon unit. Independent work carried out by Czech researchers[41] using propionic acid-1-^{14}C and by Corcoran and coworkers[42] using propionic acid-1-^{14}C, -2-^{14}C, and -3-^{14}C led to the same conclusion.

Scheme 1 [a]


70
1) hydrolysis
2) IO_4^-
Kuhn-Roth oxidation
$CH_3CH_2CHO + CH_3COOH$
$CH_3CH_2COOH + 6\ CO_2 + 6\ CH_3COOH$

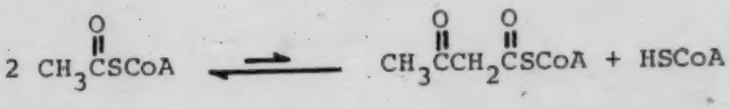
a) "★" marks the ^{14}C label; "†" marks the ^{3}H label.

In contrast to the efficient incorporation (up to 69%) of propionate in erythromycin, acetic acid-2-^{14}C is used to less than 1%[42] and complete randomization[43] of the label in the acetic acid derived from Kuhn-Roth oxidation of erythromycin is observed. These results rule out Birch's acetate hypothesis.

Formate, methionine, and succinate were also examined as carbon sources.[42b,44] Formate was not incorporated at all while methionine proved an efficient reagent only for the sugar residues. Succinate was utilized weakly but to a somewhat greater extent than was acetate.

Since a deeper understanding of macrolide biosynthesis arose directly from progress in the field of fatty acid synthesis, some brief comments concerning the production of fatty acids (*e.g.* **69**) follow. For review articles the reader is directed to reference 45.

Until the latter half of the 1960's, it had been assumed that the biologically active unit in Collie's Polyacetate Rule was the coenzyme A thiolester of acetic acid (**71**, acetyl-CoA). In the presence of β-ketothiolase, two acetyl-CoA molecules condense to form acetoacetyl-CoA (**72**). It was discovered, however, that this reversible



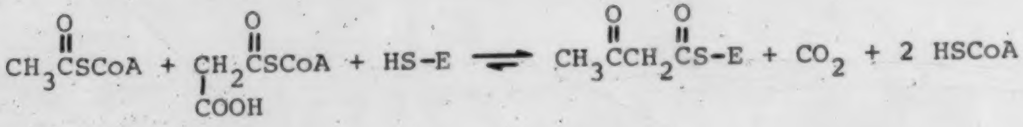
$$2\ CH_3\overset{O}{\overset{\|}{C}}SCoA \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}SCoA + HSCoA$$

71 **72**

$$K_{eq'm} = 1.6x10^{-5}$$

condensation does not accurately represent the course of acetate polymerization during fatty acid biosynthesis --a result that is not too surprising in view of the thermodynamic disfavour of the forward reaction. One of the two acetyl-CoA molecules is first converted into the more activated species, malonyl-CoA (**73**). Then, in the presence of a multienzyme complex, fatty acid synthetase E-SH (SH represents the hydrosulphide binding site), acetyl-

CoA and malonyl-CoA condense to form an enzyme-bound acetoacetate molecule (74). Reduction of the β-keto group

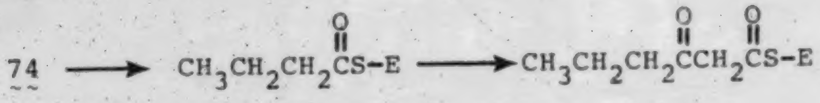


$$\mathrm{CH_3\overset{O}{\overset{\|}{C}}SCoA + \underset{COOH}{CH_2}\overset{O}{\overset{\|}{C}}SCoA + HS{-}E \rightleftharpoons CH_3\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}S{-}E + CO_2 + 2\,HSCoA}$$

71 73 74

$$K_{eq'm} = 2x10^5$$

in 74 produces butyryl-enzyme (75) which may then condense with a second molecule of malonyl-CoA. The sequence of

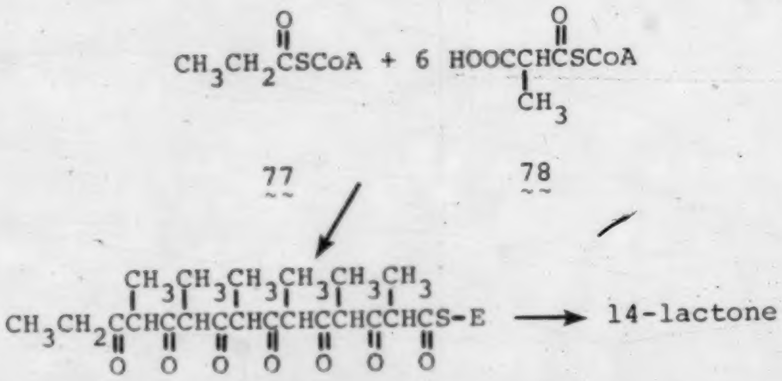


$$\mathrm{74 \longrightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}S{-}E \longrightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}S{-}E}$$

75 76

reduction and condensation continues until the enzyme complex finally releases the fatty acid. The net result is that a primer unit of acetyl-CoA marks the tail of the fatty acid, all other two-carbon units being derived from malonyl-CoA.

Lynen[45a] postulated that the lactone of erythromycin might be derived in a similar way from a primer unit of propionyl-CoA which initiates a stepwise condensation with six molecules of methylmalonyl-CoA. Carbons 13-15 of the final lactone would originate from the single propionyl-CoA unit.



$$CH_3CH_2\overset{O}{\overset{\|}{C}}SCoA + 6\ HOOC\underset{CH_3}{\underset{|}{C}H}\overset{O}{\overset{\|}{C}}SCoA$$

77 78

$$\downarrow$$

$$CH_3CH_2\underset{O}{\underset{\|}{C}}\overset{CH_3}{\overset{|}{C}H}\underset{O}{\underset{\|}{C}}\overset{CH_3}{\overset{|}{C}H}\underset{O}{\underset{\|}{C}}\overset{CH_3}{\overset{|}{C}H}\underset{O}{\underset{\|}{C}}\overset{CH_3}{\overset{|}{C}H}\underset{O}{\underset{\|}{C}}\overset{CH_3}{\overset{|}{C}H}\underset{O}{\underset{\|}{C}}\overset{CH_3}{\overset{|}{C}H}\underset{O}{\underset{\|}{C}}S\text{-}E \longrightarrow \text{14-lactone}$$

79

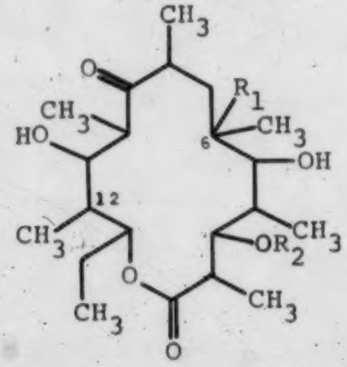
Kaneda, Friedman, and Corcoran[46] demonstrated that the preliminary processes implicit in Lynen's proposal were operative in *S. erythreus*. After incubation of propionic acid-1-^{14}C with the microorganism, the authors were able to detect the presence of methylmalonic acid-1-^{14}C. This result shows that conversion of propionate to methylmalonate can occur. The lack of scrambling suggests the conversion to be rather direct. Additional results showed that propionic acid and methylmalonic acid can be metabolized as the coenzyme A esters.

To test Lynen's theory Grisebach, Hofheinz, and Achenbach[47] incubated *S. erythreus* with propionic acid-1-^{14}C-3-^{3}H and degraded the resulting antibiotic to dihydroerythronolide (*e.g.* 70). Saponification of dihydroerythronolide followed by periodate cleavage gave C_{13}, C_{14}, and

C_{15} as propanal and C_{12} and C_{12a} as acetic acid (see Scheme 1, page 44). Of the total radioactive content (^{14}C or ^{3}H) in dihydroerythronolide, an incredible 55% was found in the propanal. Lynen's theory can explain the result by assuming that [^{14}C, ^{3}H]-propionyl-CoA initiated the biosynthesis of the lactone and that the bulk of the methylmalonyl-CoA originated from what was initially contained in the cells. To support this view, the workers found that feeding propionic acid-1-^{14}C-3-^{3}H to resting cells of S. erythreus produced erythromycin in which the radioactivity of each label was equally distributed among the seven three-carbon units. By repeating the experiment with resting cells, but adding unlabelled methylmalonic acid as well as the labelled propionic acid to the culture, the proportion of radioactivity in the propanal rose from 17 to 30%. Additional evidence was reported independently by Corcoran and coworkers.[46b]

The building blocks of erythronolide now defined, attention was directed towards the elucidation of intermediates along the biogenetic pathway. The lactones of erythromycins A and C are identical and differ from that (80) of erythromycin B by having an extra oxygen at C_{12}. Erythromycins A and B both contain D-desosamine and L-cladinose whereas erythromycin C differs from A only in the C_3 sugar, L-mycarose, the O-demethylcladinose. Wild strains of S. erythreus coproduce all three erythromycins. Therefore it was suspected that all share, by and large, the same synthesis.

Tardrew and Nymen[48] reported in 1964 the isolation of the free aglycone of erythromycin B, erythronolide B (80), from chemically mutated strains of S. erythreus that had a partial block in the biogenetic pathway to the antibiotics. For studies to determine whether 80 is a true



80: R_1=OH, R_2=H (erythronolide B)
81: R_1=H, R_2=H
82: R_1=OH, R_2=α-L-mycarosyl

intermediate, Hung, Marks, and Tardrew[49] selected a high erythromycin-producing strain of S. erythreus. During the incubation of this strain with propionic acid-1-^{14}C no evidence for the intermediacy of erythronolide B (80) could be found. However radiochromatography of the broth extract did show that a single, labelled compound I (unidentified) was formed very quickly. The total radioactive content of labelled products then stayed constant for the remainder of the incubation, during which compound **I** disappeared with the concomitant production of the erythromycins.

Nevertheless, at a certain stage during the incubation labelled **80** had been present, only in concentrations too low to be detected. This was proved by treating the microorganism with both propionic acid-1-^{14}C and a large amount of unlabelled **80**. In this way the radioactive **80** produced during the fermentation was successfully trapped in the large reservoir of unlabelled material. Again, compound **I** was formed very quickly, initially as the sole labelled product. The slow disappearance of compound **I** was accompanied by the appearance of ^{14}C-erythronolide B (**80'**). After complete consumption of **I**, the radioactive content of **80'** was essentially the same as that initially held by **I**. Only after the complete disappearance of **I** were erythromycins detected.

The same workers further showed[49] that ^{14}C-labelled **80** (**80'**) was converted efficiently and quantitatively by *S. erythreus* to a mixture of all three erythromycins (see Table 1). A study of the intermediary metabolism of ^{14}C-erythromycins A and B suggested a secondary

Table 1: Interconversions[a,b] of Erythromycins A, B, and C and Erythronolide B.

Substrate	% Conversion				
	Erythromycin			Compound	
	A (7')	B (8')	C (9')	II'	III'
^{14}C-erythronolide B (80')	45.2	14.5	28.6		
^{14}C-erythromycin A (7')	23.9	0	29.1	46.1	0
^{14}C-erythromycin B (8')	19.5	67.2	0	0	13.1

a) The length of incubation was 24 hr.

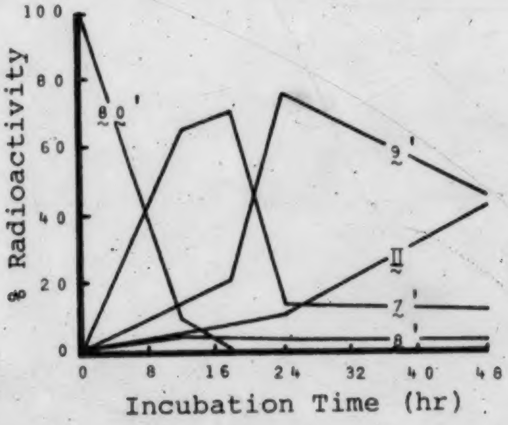
b) The prime notation is used to indicate radioactivity.

irreversible pathway to erythromycin A, via erythromycin B. Mechanistic information was also provided by a kinetics study of the metabolism of 80' (see Figure 4). During the kinetics experiment none of the radioactivity was lost.

On the basis of the observations outlined above, Hung et al.[49] proposed a crude model for erythromycin biosynthesis. The notation used in Scheme 2 is an adaptation of that introduced by Corcoran and Chick.[50]

The possibility that certain steps might be reversible was not considered although the results can equally as well be explained by replacing the hydroxylation step in Scheme 2 with a reversible interconversion

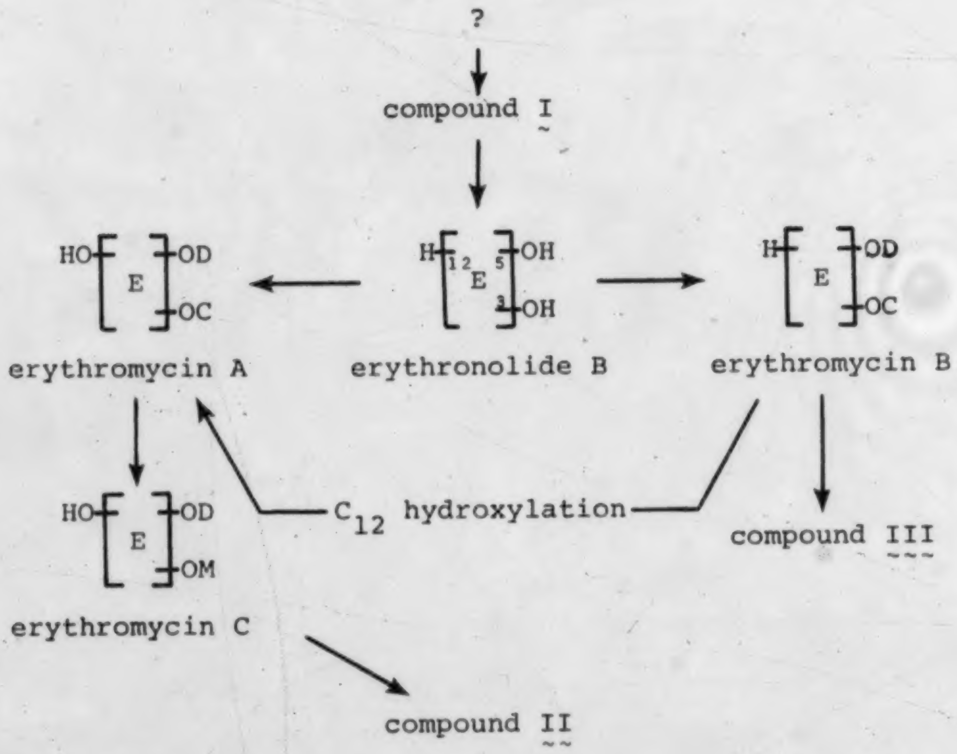
Figure 4: Metabolism of ^{14}C-Erythronolide B



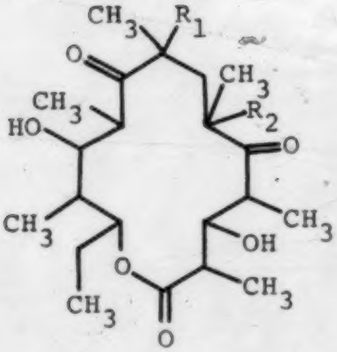
of erythronolide B and erythromycin B. Also Scheme 2 represents only the major biosynthetic pathways. The presence of minor routes cannot be excluded. In fact the sensitivity of the ratios and yields of the erythromycins to the culture make-up, to the mutant strain, and to the day of the week may result from a minor pathway in one strain becoming dominant in another.

Other macrocyclic lactone metabolites (81-85) have been isolated from various partially blocked and totally blocked mutants of S. erythreus.[51] Martin and coworkers claimed that two of these lactones, namely 6-deoxyerythronolide B (81) and 3-α-L-mycarosylerythronolide B (82), are true intermediates of biosynthesis.[51a,b]

Scheme 2


?
compound I
erythromycin A
erythronolide B
erythromycin B
erythromycin C
C12 hydroxylation
compound III
compound II
HO
OD
OC
OM
E
H
OH
1
2
5
3

Compound 81 was thought to be the immediate progenitor of erythronolide B (80), the transformation involving the introduction of the extra oxygen at C_6. Lactone 82 would then follow from 80. Intermediacy of 81 and 82 was concluded on the strength of the observation that each was converted to erythromycin A when fed to *S. erythreus* with an early biogenetic block. As no erythromycins were detected during similar experiments with 83-85, these



83: R_1=H, R_2=OH
84: R_1=H, R_2=H
85: R_1=OH*, R_2=H

were considered to be shunt metabolites.

A route to erythromycins through 81 is biochemically pleasing but involvement of 82 poses a problem since it is in direct opposition to Hung's earlier proposal (Scheme 2). However the intermediacy of 81 and 82 should only be regarded as speculative for the following reasons. The metabolic consequences of 81 and 82 were only reported using highly abnormal strains of the microorganism--strains that had been chemically mutated in a highly non-selective manner. There is no guarantee that the conversion to erythromycins of metabolites fed to such strains any longer follow the same sequence of steps occurring in non-blocked S. erythreus. In fact the rather slow conversion rates of **81** and **82** observed might reflect a significant difference. Secondly, Martin *et al*. did not use radioactive **81** and **82** in their studies. Analysis was by tlc and bio-assay. Accordingly they were unable to fully account for substrates consumed and some results were only qualitative. Since both Hung's and Martin's research groups worked at Abbott Laboratories, North Chicago, it is unfortunate that Martin and coworkers did not study the metabolism of labelled **81** and **82** on the same strain of *S. erythreus* as employed by Hung's group. No mention was made of the possible identity of Hung's compound **I** and **81**.

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*Oleandomycin, lankamycin, and 85 all have the same absolute configuration at C_8.

Scheme 3

$$\begin{tikzcd}
 & \text{compound I (81?)} \arrow[d] \\
\text{82} \arrow[r, shift left] & \text{erythronolide B (80)} \arrow[l, shift left] \arrow[d] \\
 & \text{erythromycins}
\end{tikzcd}$$

On the evidence at hand, Hung's and Martin's data can be brought into accord by assuming that **82** is not an intermediate but arises from a reversible shunt from **80** (Scheme 3). The involvement of the shunt could be tested by examining the fate of 3-α-L-mycarosyl(C_3,-$^{14}CH_3$)-erythronolide B-^{3}H (**82'**) in which the sugar moiety specifically carries ^{14}C and the aglycone specifically carries tritium. Such a compound could be prepared by simultaneously treating an 82-producing mutant of S. erythreus with propionic acid-3-^{3}H and methionine-$^{14}CH_3$*. If there were no significant decrease in the ^{14}C:^{3}H ratio accompanying the transformation of 82' to the erythromycins, the intermediacy of 82 would be all but proved and Scheme 3 must be discarded.

In a third study on a particular mutant of S. erythreus, no history of which was reported, conducted by Spizek et al.,[52] the predominant pathway to erythromycin C appeared to bypass 80.

The most fascinating area of macrolide biochemistry has remained unexplored. How does the singular nature among all macrolides of the lactone stereochemistry (see Chapter 2) relate to the biosynthesis? No facts are available at the present time.

Biogenesis of Macrolide Sugars

The deoxygenated nature of the macrolide sugars originally led Woodward[5] to suggest that the similarities in the structural appearances of the sugars and the lactones may be more than just superfacial and may reflect a biogenetic origin of the sugars from processes analogous to those involved in building the lactones.

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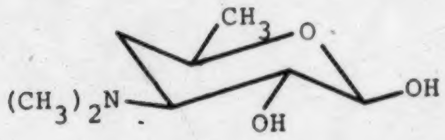
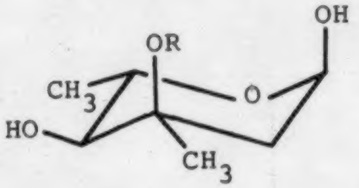
*Methionine was known to be an efficient source for the C_3-methyl in cladinose (see Biogenesis of Macrolide Sugars, Chapter 3).



13: β-D-desosamine



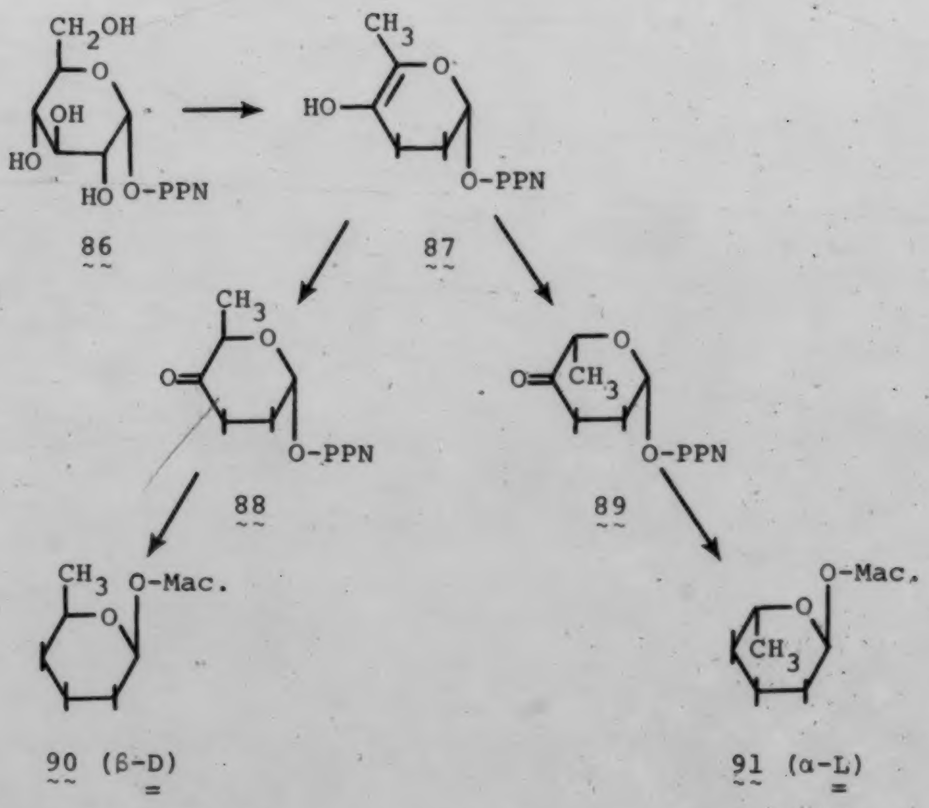
16: R=CH_3; α-L-cladinose

17: R=H; α-L-mycarose

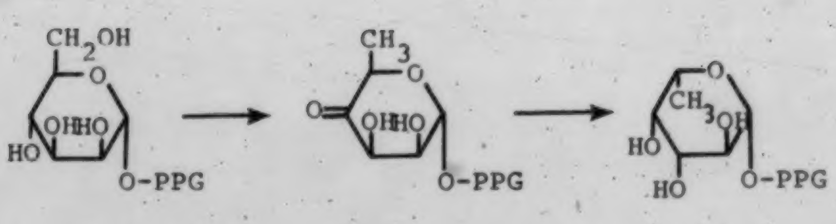
Whereas L-methionine-$^{14}CH_3$ was shown not be to involved in the biosynthesis of methynolide or erythronolide, incorporation of the methyl group from the amino acid into the sugars, desosamine and cladinose, was efficient.[53,44,55] Degradations established that in desosamine all radioactivity was located in the dimethylamino function whereas in cladinose the label was equally distributed between the O-methyl and the C-methyl at C_3. Furthermore, contrary to Woodward's suggestion, convincing evidence[56] has been reported that desosamine and cladinose are derived directly from D-glucose, a standard nutrient of culture media. Thus when *S. erythreus* was incubated with D-glucose-1-^{14}C, -2-^{14}C, or -6-^{14}C, the bulk of the label was found at the corresponding carbon of desosamine. Consequently the integrity of the carbon skeleton must be preserved during the transformation of glucose into 13. Similar results suggest that cladinose is also derived directly from glucose. It is logical to assume that cladinose and mycarose share much of their biogenesis.

It was mentioned in Chapter 2 that the sugar residues in all macrolides have the same absolute configuration at their anomeric centres. To account for this using glucose as the common starting material, Celmer[23,27] proposed that D-glucose is bound to a nucleotide, represented in Scheme 4 as a diphosphate nucleotide (PPN), during its conversion to the macrolide 6-deoxy sugars. The nucleotide is retained in the intermediates until the final transfer to the macrocyclic lactone. This theory is based on certain known facts.[57] 4-Keto-6-deoxy sugars have been shown to be intermediates in the biosynthesis of non-macrolide 6-deoxy sugars. For example,[58] an enzyme preparation from *Aerobacter aerogenes* converts 1-guanosine-5'-diphosphate-D-mannose (92) to 1-guanosine-5'-diphosphate-L-fucose (94) via 93.

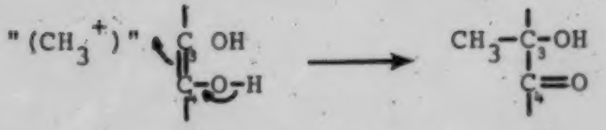
Scheme 4


CH2OH
O
OH
HO
HO
O-PPN
86
CH3
O
HO
O-PPN
87
CH3
O
O
O-PPN
88
O
O
CH3
O-PPN
89
CH3
O-Mac.
O
90 (β-D)
O-Mac.
O
CH3
91 (α-L)

The amino group in desosamine might be introduced by transamination using an intermediate 3-keto-6-deoxy sugar. Grisebach[59] has suggested that C-methylation leading to cladinose and mycarose may proceed through an endiol (95).


CH2OH
O
OH
HO
HO
O-PPG
CH3
O
O
OH
HO
O-PPG
O
CH3
OH
HO
HO
O-PPG

92 93 94


"(CH3+)"
C
OH
C
O-H
CH3
C
OH
C
O

95 96

CHAPTER 4

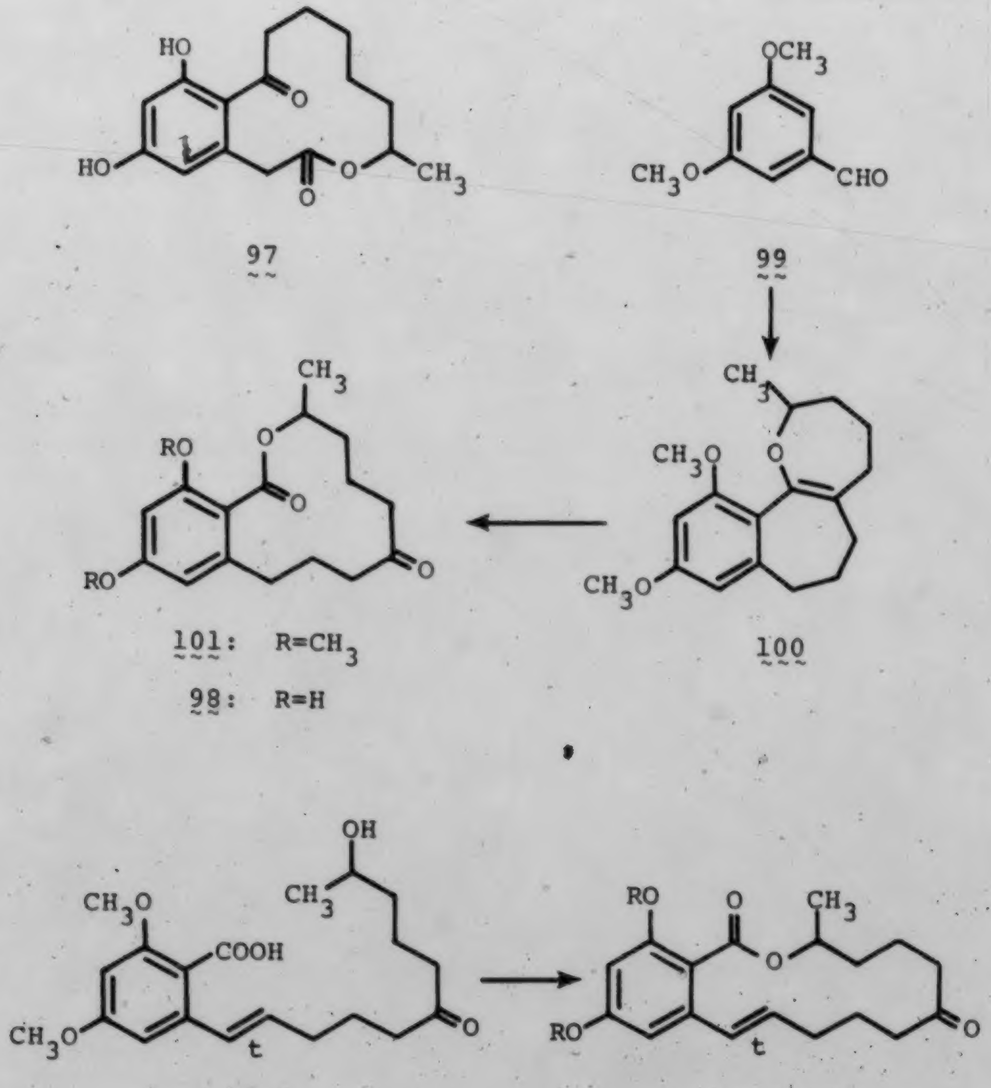
PREVIOUS SYNTHETIC STUDIES OF MACROLIDES

During the last four years several pseudomacrolides have been synthesized. However none of these substances possess the extreme degree of substitution that is characteristic of the nonpolyene macrolides.

A structural isomer (98) of curvularin (97) was synthesized by Bagli and Immer in 1968.[60] As the key step in the sequence, they employed a lactone synthesis first developed by Borowitz and Gonis,[61] in which the tricyclic vinyl ether 100 was oxidatively cleaved by *m*-chloroperbenzoic acid to 101. Removal of the O-methyl groups afforded 98.

Several successful syntheses[62] of the 14-pseudomacrolide, (+)-zearalenone (104), have appeared in literature. In two reports[62a,c] the final steps involve a low-yield (10%) lactonization, catalysed by trifluoroacetic anhydride, followed by cleavage of the O-methyl ethers.

Recently Raphael and coworkers[63] have reported the first preparation of a nonaromatic macrolide, (±)-pyrenophorin (106). Execution of a series of straightforward reactions led to 105. Conversion of 105 to the acyl imidazolide followed by treatment with base



97

99

100

101: R=CH_3

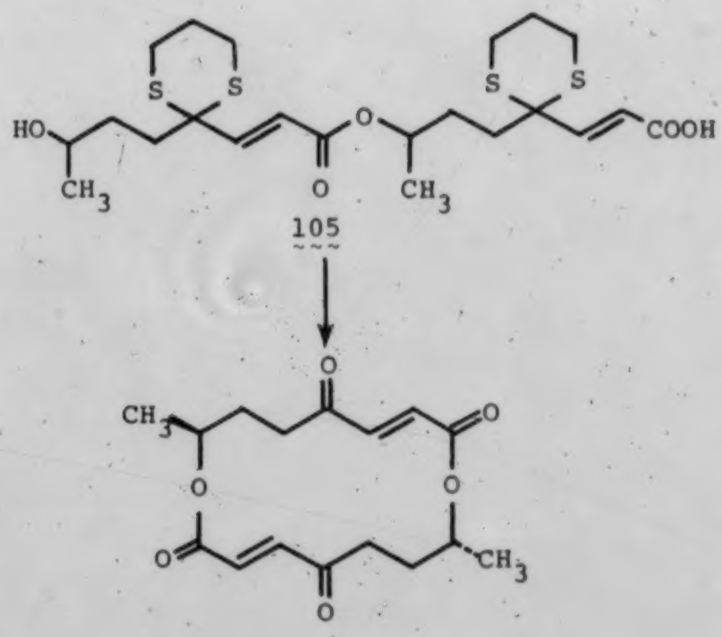
98: R=H

102

103: R=CH_3

104: R=H

HO
HO
O
O
O
CH_3
OCH_3
CH_3O
CHO
CH_3
RO
RO
O
O
O
CH_3
CH_3O
CH_3O
O
OH
CH_3
CH_3O
CH_3O
COOH
t
O
RO
RO
O
CH_3
O
t
O

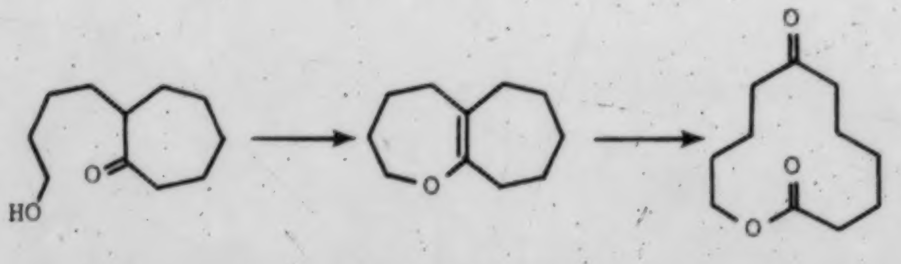


105

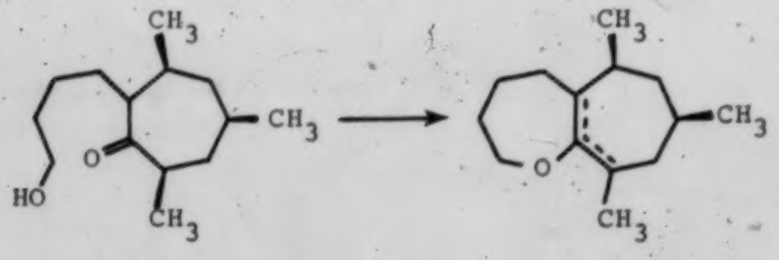
106

effected cyclization in 60% yield, giving a 1:1 mixture of diastereoisomers. After hydrolysis of the thioketals and removal of the *meso* product, (±)-pyrenophorin (106) remained.

Borowitz and coworkers[64] have extended their investigation of the oxidative cleavage of vinyl ethers to determine the feasibility of the approach towards generating the lactone system of methymycin. As exemplified by the synthesis of 7-oxoundecanolide (109),[65] their procedure requires first the C-alkylation of a cyclic ketone with a suitable difunctional reagent and then the



107 108 109

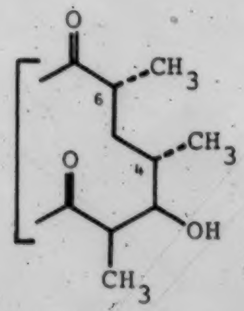


110 111a,b,c

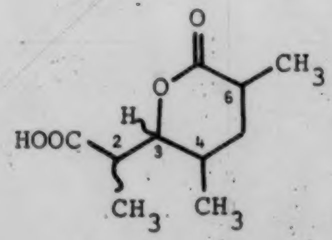
conversion of the free terminus of the alkyl side chain into a hydroxyl. Acid-catalysed dehydration leads to the vinyl ether. Besides the capricious nature of the alkylations, the workers found that the dehydrative cyclization of a four-carbon side chain (as in 107) does not proceed well. This is especially true if the starting ketone carries substituents. Thus in the case of 110, cyclization "occurred to a minor extent", affording a mixture of three isomeric enol ethers, presumed to be 111a,b,c. The authors concluded that the present synthesis of cyclic vinyl ethers cannot be applied to the preparation of complex macrolides.

The most significant work dealing with the synthesis of highly substituted macrolides originated from

Russia.[18,66-68] Surprisingly this work is quite old, first started in 1962 and apparently concluded by 1966. When the Russian team, headed by Bergel'son and Batrakov, initiated its study, the only stereochemical information known about methynolide and neomethynolide (partial structure **112**) was the configurations 4*S* and 6*R*.[17c,d] In order to



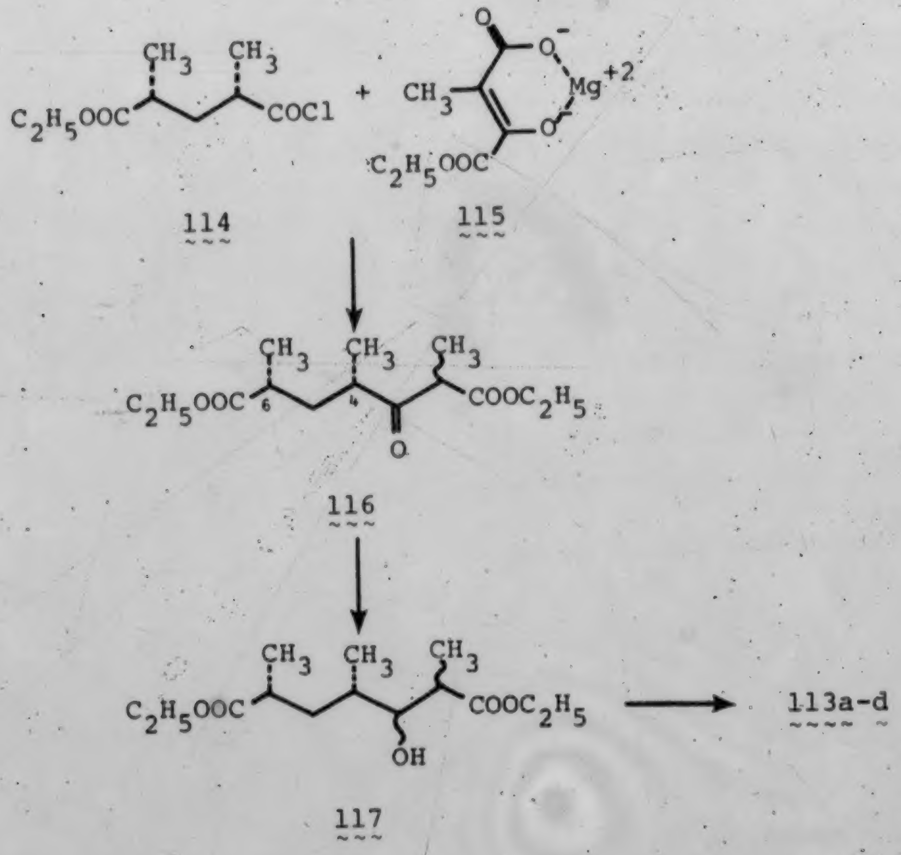
112



113a-d

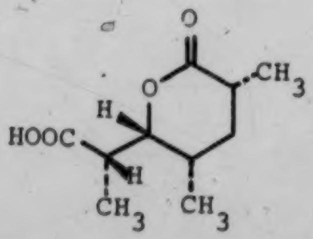
establish the stereochemistry at C_2 and C_3, they developed a synthesis of all four diastereoisomers of the lactonic acid **113** in which they believed that the C_4- and C_6-methyls were *cis*. Scheme 5 outlines briefly the route employed. A mixture of *meso*- and (±)-α,α'-dimethylglutaric acid was converted to the anhydride from which pure *meso*-α,α'-dimethylglutaric anhydride was obtained by fractional recrystallization. Acylation of **115** with **114**, prepared from the *meso* anhydride, gave **116**. The lactonic acid **113** was obtained by reducing the ketone group of **116**, saponifying the esters, and acidifying. When the carbonyl

Scheme 5



of 116 was hydrogenated over Raney nickel or chromium-nickel catalysts, 113a and 113b resulted in 10 and 35% yields respectively. On the other hand, lactonic acid 113c (25% yield) was formed when 116 was reduced with lithium triethoxyaluminum hydride. Lithium aluminum hydride reduction led to 113d (58% yield). Bergel'son and Batrakov stated that 113d was the racemic form of the Djerassi-

Prelog lactonic acid (+)-32. The identity of the two compounds was based solely on the solution ir spectra of their corresponding methyl esters. In a subsequent paper,[18b] nmr analysis and degradation studies of 113d convinced the Russians that the product had the structure indicated below. Accordingly they assigned the configurations 2S and 3R to (+)-32 (and hence to methymycin and neomethymycin).



113d

As mentioned in Chapter 1, Rickards and Smith[11a] demonstrated later that the chirality at C_2 and C_3 in the 12-macrolides is in fact the reverse. Since the chemical evidence presented by the Russians for the relative stereochemistry of C_2 and C_3 in 113d is strong, it appears that 113d must not be the racemate of "natural" (+)-32. In fact a comparison of the ir spectra of their methyl esters, reproduced in the original article,[18a] shows differences that cannot be attributed to solvent effects. Based on the experimental information available, it is impossible to decide at precisely which stage they were misled.

Nonetheless a general comment can be made.

In at least two reactions of Scheme 5, epimerization of a methyl group originating from the meso anhydride should be considered a possibility. The catalytic hydrogenation of **116** was carried out in aqueous ethanol at elevated temperatures (90° and 120°). Under these conditions significant epimerization of the C_4-methyl might have preceded reduction, particularly so if the surfaces of the catalysts were not neutral. Secondly, epimerization of the C_6-methyl of **117** could have occurred during the saponification of the ethyl esters. The diester **117** was hydrolysed using potassium hydroxide in 80% aqueous ethanol, stirred overnight at room temperature and then for three hours at 45°. In a similar case Wiley *et al.*[7] heated the dilactone **118**, derived from erythromycin A, with 1.0 *M* aqueous sodium hydroxide on a steam bath for four hours. It is apparent now that at least 50% racemization* of the C_8-methyl occurred during hydrolysis.

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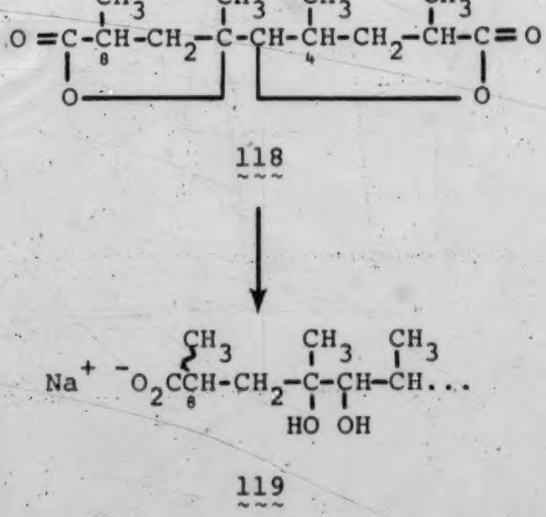
*This value was arrived at by considering optical rotation data of various preparations of (-)-α-methyllevulinic acid 2,4-dinitrophenylhydrazone, reported in references 7 and 17d.



118

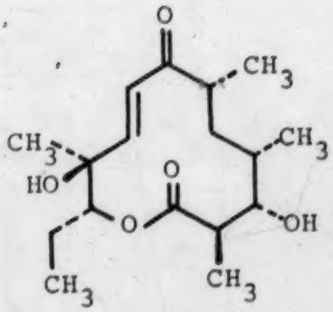
119

CHAPTER 5

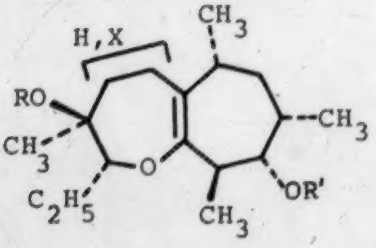
AN APPROACH TO THE SYNTHESIS OF METHYMYCIN

It has been the aim of the introductory chapters to demonstrate how integrated the chemistry and properties of all macrolides are. The common stereochemical features of the macrolide aglycones are especially interesting. Because of both the practical and the theoretical interest in the macrolide antibiotics, we were prompted to initiate a synthetic study. A first successful synthesis might ultimately lead to a general scheme for synthesis which, through simple modifications, would permit the construction of highly substituted lactones of various ring sizes, with any desired sequence of substituent configurations. Such a scheme would no doubt be useful for biochemical studies of macrolides. Furthermore, certain portions of the scheme would have obvious importance in general synthetic organic chemistry.

The simplest of the multisubstituted macrolides, methymycin, was chosen as the goal of our synthesis. The work reported in this thesis is concerned with the synthesis of methymycin's aglycone fragment, methynolide (**25**). There are several possible approaches to the building of **25**.



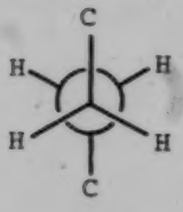
25



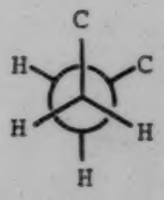
120

One method involves the construction of a polycyclic system which carries all of the substituents of methynolide. In the latter stages of synthesis, the key reaction becomes the splitting of the polycyclic structure into the monocyclic twelve-membered lactone. This was the approach taken by Borowitz and associates[64] and by Bagli and Immer[60] (see Chapter 4). A compound suited for peracid cleavage might resemble 120. Although oxidation of the central double bond might be expected to proceed in fairly good yield, the synthesis of 120 would be very troublesome. At the present time the control that chemists have over reactions involving seven-membered rings is much less than for smaller ring systems. In addition, the introduction of the *trans* double bond by elimination of HX may not be easy. Other modes of converting a polycyclic system to a twelve-membered lactone are possible but in each case construction of the necessary precursor would be exceedingly difficult. Any generalization of a successful synthesis to other macrolides would be impossible.

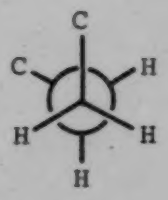
A second approach to the building of methynolide is the construction of the medium ring at an early stage, followed by the elaboration of the substitution pattern around the ring. The success of such a strategy would rely upon an intimate understanding of the conformations of twelve-membered rings for any degree and pattern of substitution. In unsubstituted medium and large cycloalkanes, the preferred conformations seem to be determined largely by the torsional angle strain (Pitzer strain).[69,70] The *trans* conformation ($\underline{t}$) of skeletal carbons and the less energetically favoured *gauche* conformations ($\underline{g}^{\pm}$) are shown below in Newman projection. Minimization of Pitzer strain



$\underline{t}$

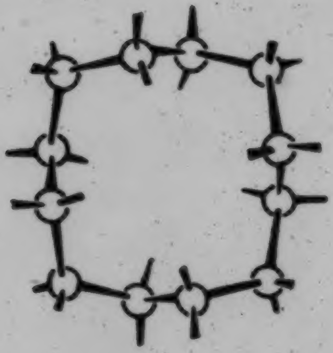


$\underline{g}^{+}$



$\underline{g}^{-}$

determines, by and large, the approximate shape of the cycloalkane. Consideration of transannular interactions then leads to slight distortions of the ring through bond angle deformations (Baeyer strain) and possible relaxation of the mm2 symmetry of the methylene units. The skeletal conformation of cyclododecane [$(CH_2)_{12}$-A], determined by X-ray analysis,[71] is shown as 121. In the schematic representation of the cyclododecane conformation, the "o"-positions define a plane of methylene units in the ring system. The notation "+" or "-" indicates whether each of the remaining ring methylenes lies above or below the "o"-plane. The conformation 121 also applies to simple derivatives of cyclododecane, both in the solid state and in solution. Unfortunately conformational predictions in the case of highly substituted cyclododecanes is impossible at present.

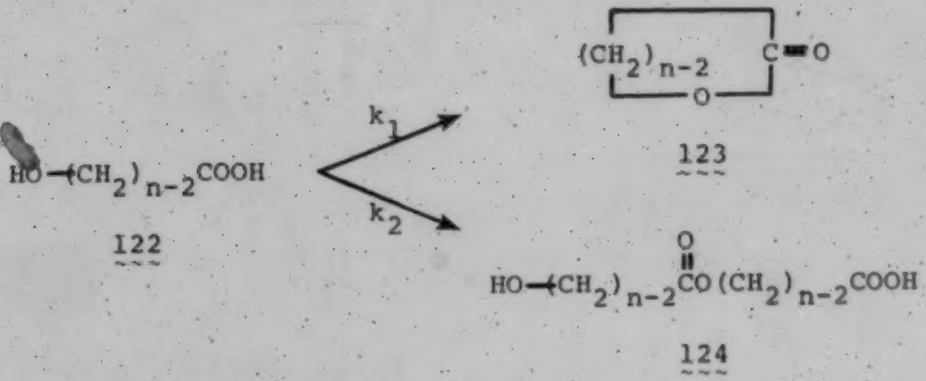


o + - o
- +
+ -
o - + o

$(CH_2)_{12}$-A

121

The third obvious route to methynolide relies upon the cyclization of an appropriately substituted, long-chain compound. The formation of medium rings* is notoriously difficult. M. Stoll and coworkers[72] carried out extensive work on the lactonization of ω-hydroxycarboxylic acids. The most serious complication arises from


$(CH_2)_{n-2}$ C=O O
123
$HO-(CH_2)_{n-2}COOH$
122
k_1
k_2
$HO-(CH_2)_{n-2}\overset{O}{\overset{\|}{C}}O(CH_2)_{n-2}COOH$
124

intermolecular condensations producing linear esters (e.g. 124). Stoll defined the ratio of the rate constants for intramolecular reaction and intermolecular reaction as the cyclization constant C. The value of C may be regarded as

$$C = \frac{k_1}{k_2}\ .$$

the concentration of 122 at which intramolecular and intermolecular reactions are equally probable. Figure 5 summarizes Stoll's results as reported by Sisido.[73] An inspec-

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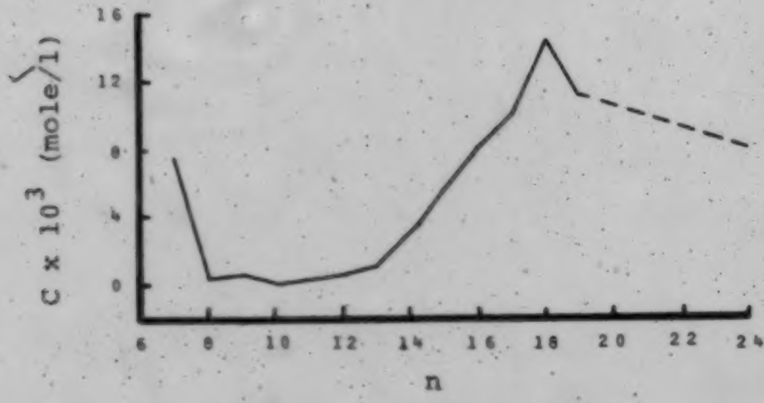
*The size of medium rings is defined as from 8 to 12. Some workers now prefer to classify the twelve-membered system as a large ring.

Figure 5: Dependence of the Cyclization Constant (C) upon the Size (n) of the Lactone



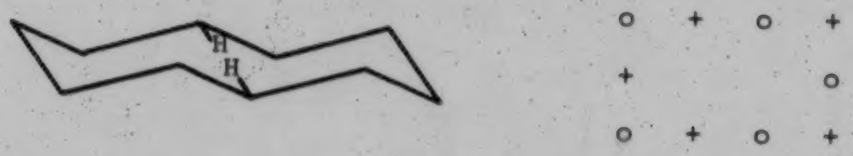
tion of Figure 5 reveals that good yields of the medium lactones are only obtained under high-dilution conditions. For synthetic work such conditions may be impractical. The following brief discussion deals with the factors that cause the yields of medium rings to be lower than those of small or large rings. A more extensive review is presented in references 69 and 70.

An aliphatic chain, X-$(CH_2)_n$-Y, can cyclize only if the ends of the chain are in close spacial proximity to each other. Consequently, irrespective of the mechanistic details of the cyclization process, the ease

7

of ring formation depends largely upon the probability that the two ends approach each other in a way conducive to reaction. Since this probability is much less for a chain of twenty-four carbons than for one of only six carbons, it might be expected that the facility of cyclization would decrease in a gradual manner as the size of the ring $(CH_2)_n$ formed increases from n=5,6,7 into the higher analogues. The yields however are also affected by the total ring strain in $(CH_2)_n$. To obtain a qualitative picture of ring strain, the diamond lattice has proved a useful model.[69a,c,70]

If a particular ring can be superimposed on the diamond lattice such that all ring carbons lie on lattice points, then the resulting conformation of the ring is free of Baeyer strain. Pitzer strain is of course still present but the diamond lattice limits the carbon-carbon torsional interactions to pure *gauche* ($g^{\pm}$) and pure *trans* (*t*). Of the possible lattice conformations for a ring, only those with the minimum number of *gauche* interactions are considered, and of these, some can be immediately discarded because of intolerable transannular repulsions [*e.g.* conformation $(CH_2)_{10}$-A for cyclodecane, **125**]. For cyclotetradecane and all larger, even rings [$(CH_2)_{2m}$, $m>7$], lattice conformations are possible in which two zig-zag chains are linked at their ends by bridges, each of two or

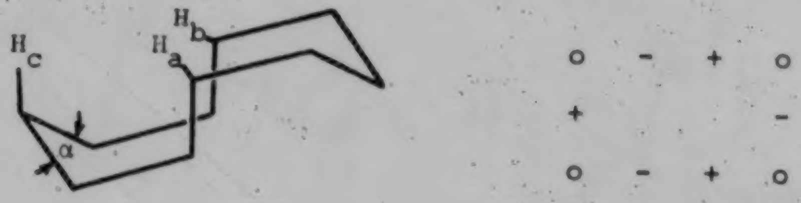


$(CH_2)_{10}$-A

125

more methylene units. In these cases, transannular repulsions, as well as Baeyer and Pitzer strains, are small. These rings are regarded then as "strain free".

For even rings between cyclohexane and cyclotetradecane, two zig-zag chains can be joined only by one-methylene bridges. The results can be seen in the conformation $(CH_2)_{10}$-B for cyclodecane. Very strong repulsions

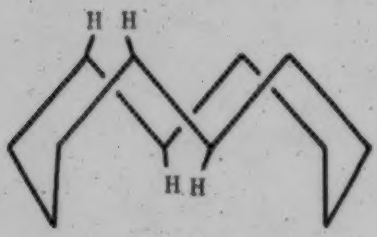


$(CH_2)_{10}$-B

126

exist between the hydrogens H_a, H_b, and H_c. No more favourable lattice conformation can be drawn for cyclodecane. The consequence, determined by X-ray analysis,[69c] is a conformation $(CH_2)_{10}$-C in which there has been some relief of the transannular strain associated with 126 through a widening of all internal bond angles. In this distorted lattice conformation $(CH_2)_{10}$-C, the bridging angle (α) has been increased to 119° and the separation of protons H_a and H_b has been extended to approximately 1.85 Å, still much shorter than the van der Waals separation of 2.4 Å. The sequence of trans and gauche interactions is unaffected. The conclusion is reached that cyclodecane is highly strained.

Cyclododecane has a most favoured lattice conformation $(CH_2)_{12}$-B, which is similar to $(CH_2)_{10}$-B.[70] In this case, the two additional methylene groups give cyclododecane sufficient flexibility to assume the off-lattice conformation $(CH_2)_{12}$-A (121), in which the two zig-zag chains are joined by two-carbon bridges, thus greatly relieving transannular strain. Since $(CH_2)_{12}$-A cannot even approximately be placed on the diamond lattice, the conformation contains significant Baeyer strain. On the



o + o + o
-   -
o + o + o ,

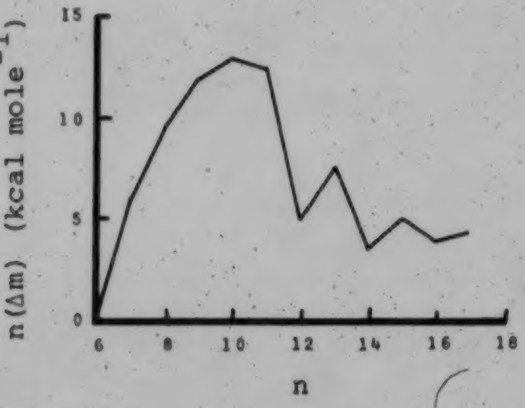
$(CH_2)_{12}$-B

127

other hand, $(CH_2)_{12}$-A has no eclipsed carbon pairs and has as few gauche interactions as $(CH_2)_{12}$-B. On the basis of the much smaller intramolecular repulsions in $(CH_2)_{12}$-A compared to $(CH_2)_{10}$-C, cyclododecane would be expected to be the less strained.

No cycloalkane with an odd number of methylene groups can be superimposed on the diamond lattice.[70] None therefore is "strain free". As the size of the ring increases though, the strain energy per methylene subunit becomes less.

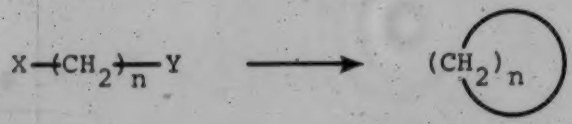
Figure 6: Thermochemical Strain in Cycloalkanes $(CH_2)_n$



Δm: the difference in the heat of combustion (liquid) between one ring-methylene group of $(CH_2)_n$ and an aliphatic methylene group.

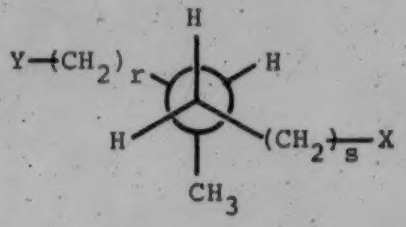
The above discussion of ring strain explains qualitatively the experimental results depicted in Figure 6.[69b]

Because of the strain inherent in the medium rings, the ends of a polymethylene chain, $X-(CH_2)_n-Y$, $n=8,\ldots,12$, cannot lie close to each other without the chain experiencing Baeyer strain and perhaps intramolecular repulsions. The amount of strain assumed by the chain prior to cyclization depends upon the size of the ring being formed. For longer chains ($n>12$), the strain is much less. As implied in Figure 6, experimental results show that nine-, ten-, and eleven-carbon chains are the most reluctant to close (cf. Figure 5). Also, in the large rings the greater strain of the odd-carbon members parallels their somewhat lower yields from cyclization processes.[74]

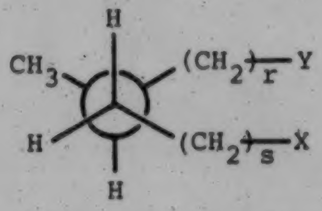


Recently Sisido[73] applied a statistical treatment to polymethylene chains, using Flory's *gauche*-*trans* rotational isomer model,[75] and successfully reproduced both the salient features of Figure 5 and the alternating high-low yields from the cyclization of even- and oddmembered large chains.

Although the yields of medium rings from cyclization procedures are usually low, we felt that a highly substituted chain in the methynolide synthesis might be more conducive to cyclization than Stoll's unbranched hydroxy acids. The energetically most favourable conformation of the difunctional polymethylene chain $X-(CH_2)_n-Y$ is the (*t*,*t*,*t*,...) or zig-zag. However for conformations suitable for ring closure, the chain must bend at several points, giving rise to *gauche* interactions. Flory assigned to a *t*,$g^{\pm}$,*t* sequence an energy 500 cal/mole higher than the *t*,*t*,*t* pattern. Now if the polymethylene chain contains one or more branches, then as an approximation, the zig-zag form 128 and the conformation 129 are equally likely. Hence the probability of kinks in the chain is greater, thereby enhancing the chances of intramolecular reaction.

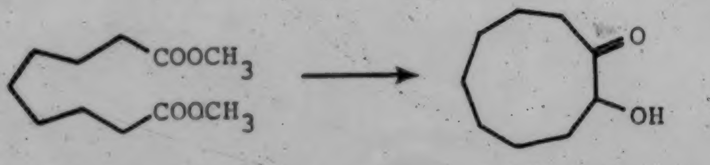


128



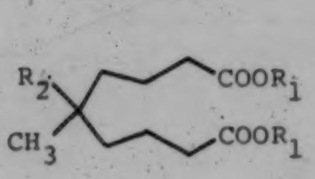
129

Experimental results bear this out. Blomquist and coworkers[76] found that, whereas the acyloin condensation of dimethyl azelate (130) produces 2-hydroxycyclononanone (131) in 35-40% yield, dimethyl δ-methylazelate (132) cyclizes in 60% yield. Moreover, diethyl δ,δ-dimethylazelate (133), in which the probability of a kink is further increased, leads to a 66-70% yield of the corresponding azeloin. The tetramethylazelate 134 cyclizes to the extent of 84%. In another example,[77] Ziegler cyclization of 135 goes quantitatively. Ring closure of 1,7-dicyanoheptane proceeds in only 30% yield. A pair of diastereoisomeric, polysubstituted chains, which exhibit remarkable differences towards intramolecular reaction, has been


COOCH3
COOCH3
O
OH

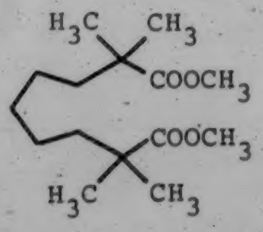
130

131

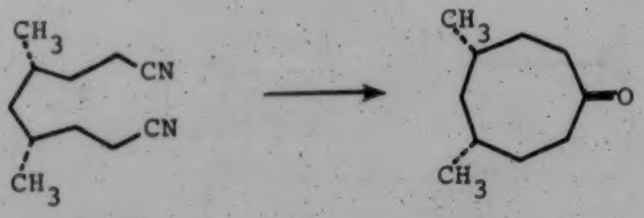

R2
CH3
COOR1
COOR1

132: $R_1=CH_3$, $R_2=H$

133: $R_1=C_2H_5$, $R_2=CH_3$


H3C
CH3
COOCH3
COOCH3
H3C
CH3

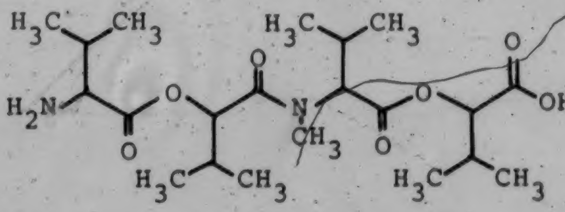
134


CH3
CN
CN
CH3
CH3
O
CH3

135

136

reported. In a brief communication Russian workers[78] stated that the tetradepsipeptide D,D,D,D-137 affords only



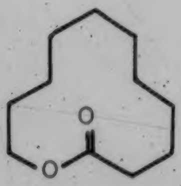
D,D,D,D-137

L,D,L,D-137

an 8% yield of the corresponding cyclotetradepsipeptide. Thirteen percent of the cyclic dimer is also formed. In contrast, the L,D,L,D-isomer gives cyclotetradepsipeptide in 70% yield as the sole product.

Considering the above evidence, it was hoped that a highly substituted aliphatic precursor to methynolide would cyclize with equally as remarkable facility.

Any potential structural instability in methynolide (25) must be assessed. One of the most striking features is the γ-(tertiary hydroxy)-α,β-unsaturated ketone. This grouping can be regarded more simply as an extension of an α-(tertiary hydroxy)ketone, which should be quite stable to both acids and bases. The stability of the lactone linkage towards hydrolysis is difficult to judge. In this connection however, the saponification of cycloundecanolide (138) with sodium hydroxide in aqueous dioxane at 0° is slow, the rate constant being comparable with that of a simple ester.[79] The β-hydroxy ester grouping should sur-



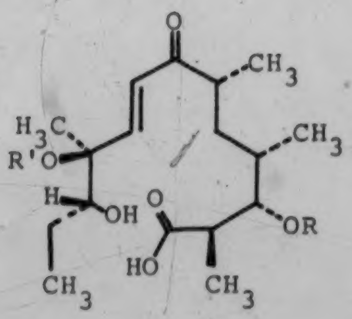
	138	*n*-butyl hexanoate
$k_2 \times 10^4$ ($l\ sec^{-1}\ mole^{-1}$)	3.3	8.4

vive mild acid and base, particularly so since no reasonable conformation of methynolide allows an anti-periplanar relationship of the hydroxyl and the α-proton. Unfortunately such insensitivity towards experimental conditions is likely not extendible to the configuration of the C_6-methyl group. This weakness in methynolide necessitates the use of a cyclization procedure that can be performed under non-enolizing conditions. We believe that two methods for ring formation offer special promise.

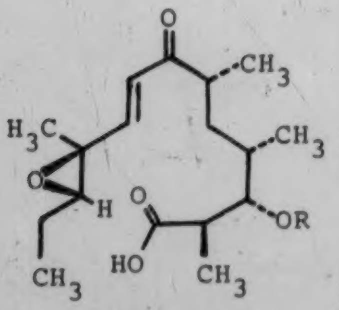
Type A Ring Closure

The first approach involves the intramolecular condensation of a carboxy group at C_1 with a C_{11}-hydroxyl (or its equivalent). Two possible immediate precursors

(139 and 140) to the ring are shown below. Ring formation



139



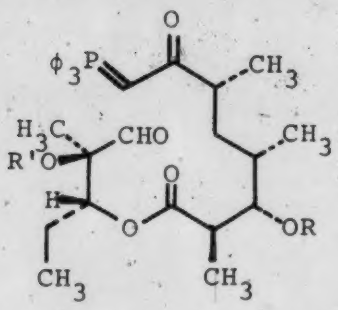
140

from 140 may proceed with or without the assistance of a Lewis acid. With care, a Lewis acid should not epimerize the C_6-methyl.

Type B Ring Closure

As the alternative method a Wittig reaction is employed to generate the unsaturated ketone moiety. The carbonyl-stabilized phosphorane 141 is a neutral substrate and should produce a double bond with the required *trans* configuration.

Unfortunately our limited supply of methymycin prevented us from degrading methynolide to compounds 139, 140, and 141 which could have been used to test the feasibility of the two approaches. Therefore model compounds were examined in their place. The results of these studies constitute the body of the following chapter.



141

Racemic Djerassi-Prelog lactonic acid (±)-32 appeared to be an ideal intermediate in the synthesis. Not only would the successful preparation of 32 complete the right-hand portion of the cyclization precursor but the chemically non-equivalent carboxy groups, a free acid and a δ-lactone, should allow fixture of the simpler left-hand portion specifically to either group, thus making the lactonic acid adaptable to both ring formation procedures. In addition, the correctness of the relative stereochemistry in the synthetic lactonic acid could be easily checked by comparing it with the "natural" (+)-32.

In conclusion the overall scheme involves: (1) the synthesis of (±)-32, (2) the construction of a suitable left-hand fragment of methynolide, and (3) the condensation of both parts followed by cyclization.

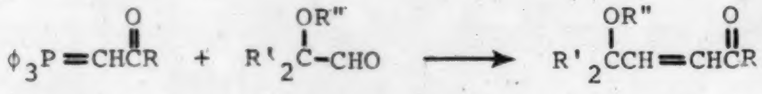
CHAPTER 6

CYCLIZATION PROCEDURES TO FORM TWELVE-MEMBERED RINGS

The extensive studies carried out by Stoll and associates[72] on the lactonization of ω-hydroxycarboxylic acids were accepted as a suitable model study for Type A ring closure. This chapter therefore describes the results of a study concerned with the practicality of an intramolecular Wittig reaction (Type B ring closure) to generate the twelve-membered ring of methynolide.

Stabilized triphenylphosphoranes, such as the acylmethylenetriphenylphosphorane **141**, react readily with aldehydes.[80] Because of the reduced electrophilic nature of the carbonyl-carbon, analogous reactions with ketones take place only under forcing conditions. It seems reasonable to expect that sterically bulky groups adjacent to an aldehyde would also impede condensation. It was therefore important to show that an aldehyde group that carries a fully substituted α-carbon, similar to the situation present in **141**, is sufficiently reactive to undergo a Wittig reaction with an acylmethylenetriphenylphosphorane.

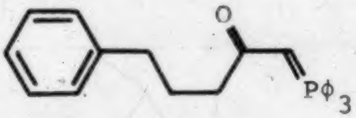
Compound **145** was selected as a suitable Wittig reagent for testing the above reaction. The intermediate phosphonium bromide 151a proved easy to prepare using



$$\phi_3P{=}CH\overset{O}{\overset{\|}{C}}R \;+\; R'_2\overset{OR''}{\overset{|}{C}}{-}CHO \longrightarrow R'_2\overset{OR''}{\overset{|}{C}}CH{=}CH\overset{O}{\overset{\|}{C}}R$$

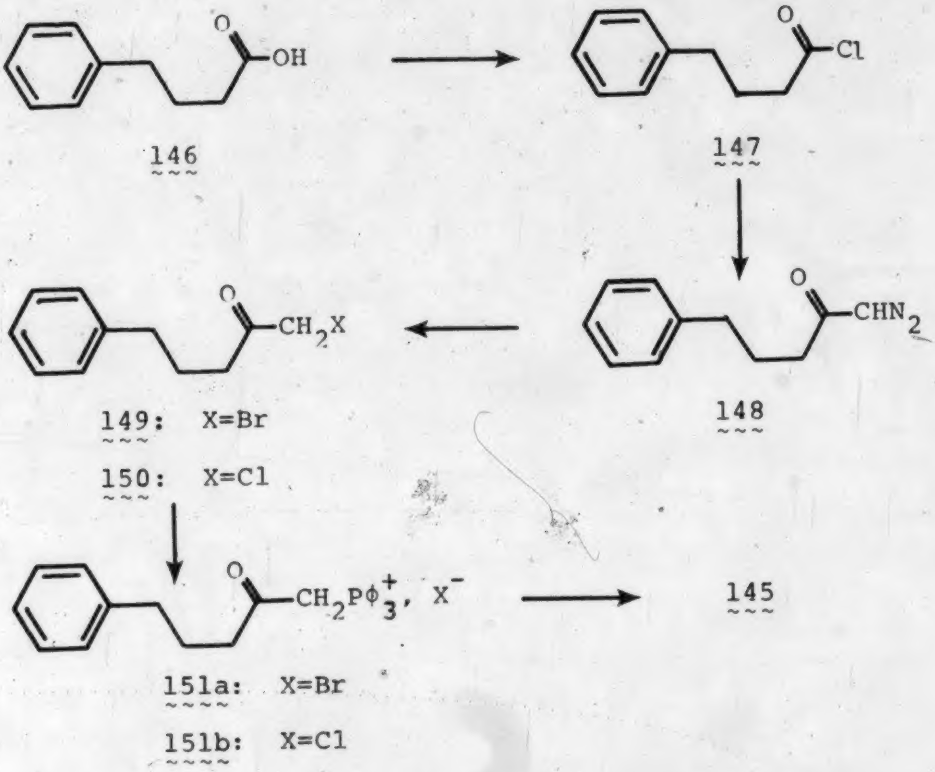
142 143 144

classical methods. Treatment of 4-phenylbutanoic acid



145

with thionyl chloride in the presence of a catalytic amount of N,N-dimethylformamide[81] afforded the acid chloride 147 in excellent yield. The slow addition of 147 to an ethereal solution containing an excess of diazomethane gave the corresponding diazoketone 148 and minimized the chance of obtaining significant amounts of 150 as a by-product. Without physical characterization the yellow diazoketone was decomposed with 48% aqueous hydrobromic acid. The resulting crude bromomethyl ketone 149 was obtained in an overall yield of 87% from 146. The nmr spectrum ($CDCl_3$) of 149 indicated the presence of some impurity. Whereas the CO-$C\underline{H}_2$-Br protons resonate at τ 6.25 as a sharp singlet, there was a second, small singlet at τ 6.07. The chemical shift ($\Delta\tau$=0.18) between these two values corres-



146

147

148

149: X=Br

150: X=Cl

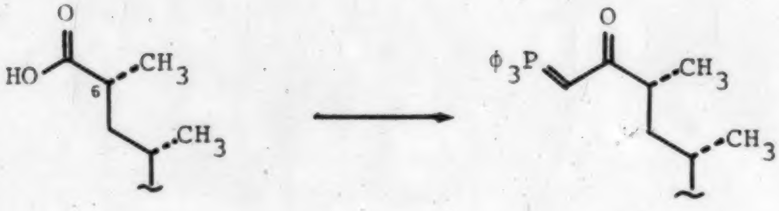
151a: X=Br

151b: X=Cl

145

ponds well with the chemical shift between the methylene protons of α-bromoacetone[82] (neat, τ 5.86) and of α-chloroacetone (neat, τ 5.68). On the assumption therefore that the impurity is 150, it was not expected that its presence (*ca*. 14%) would affect the final yield of phosphonium salt. Stirring a benzene solution of halomethyl ketones 149 and 150 and an equimolar amount of triphenylphosphine produced 151a (and presumably 151b) as a heavy white precipitate, isolated in 65% yield after recrystallization. Treatment of the salts with aqueous potassium carbonate generated the desired phosphorane 145.

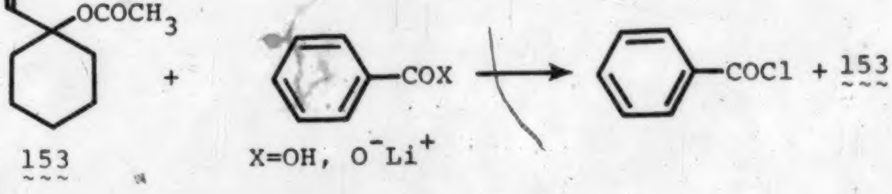
If this sequence to convert a carboxylic acid into an acylmethylenetriphenylphosphorane is to be applicable in the synthesis of 141, then certain limitations become apparent. The P-C bond in phosphoranes and phosphonium salts is sensitive to certain common organic reagents. Furthermore, purification presents another problem. Although both types of phosphorus compounds can be chromatographed on the standard adsorbants, their purification by this method may not be feasible. For instance, the dipole moment of the phosphorus-bromide bond would likely dominate in the molecular dipole moment of an organic phosphonium bromide and therefore would likely be chiefly responsible for the behaviour of the salt on various chromatographic media. The separation by this means of two phosphonium salts, one the desired product and the other a by-product, might then not be possible. For these two reasons the phosphorus group would have to be introduced during the last steps leading to 141. The bromomethyl ketone moiety is stable in neutral and mildly acidic media and to certain oxidation conditions but its reactivity towards nucleophilic reagents suggests that this functional group also must be generated near the end of the synthesis. As a consequence, the conversion of 152 to 141 must be performed under conditions as neutral as pos-



152 141

sible in order to protect the stereochemical integrity of the substrate (e.g. the C_6-methyl) and to prevent alteration of functional groups.

Appropriate modifications in the experimental procedure used in the transformation of 146 to 145 should make the reaction sequence suitable for the methynolide preparation. For example, the most severe step, preparation of the acid chloride 147, may be solved by using Lee's combination of triphenylphosphine and carbon tetrachloride[83] in the place of thionyl chloride. Although perfectly neutral the reaction is not always dependable. We have promising results that this transformation may be carried out satisfactorily employing oxalyl chloride. When benz-

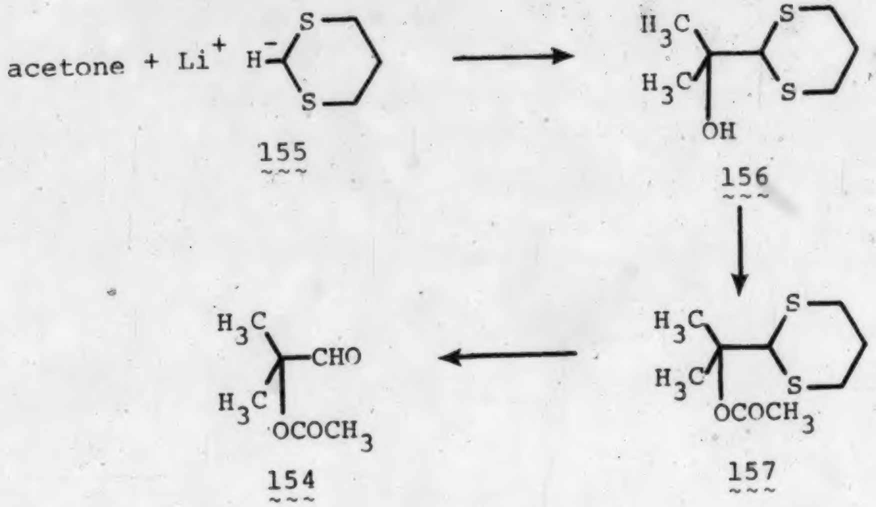


153

oic acid, in the presence of an equimolar amount of the acid-sensitive tertiary allylic acetate 153, was treated with excess oxalyl chloride in benzene, only a trace (glpc analysis; UCW-98) of 153 remained in the crude product. Treatment of a mixture of 153 and lithium benzoate with oxalyl chloride led to much improved results. Nevertheless, still *ca*. 15-20% decomposition of the allylic acetate had occurred. However by adding a drop of pyridine to the mixture of 153 and lithium benzoate, oxalyl chloride produced benzoyl chloride in quantitative yield with no detectable decomposition of the acetate.

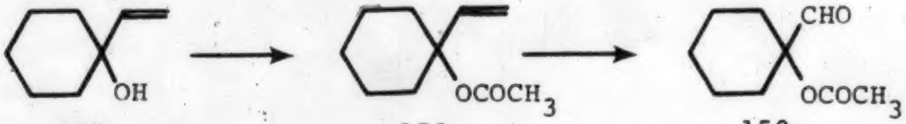
The aldehyde group in 141 poses similar problems. The general instability of aldehydes necessitates masking the group until near the end of the synthesis of methynolide. Again a neutral method to free the aldehyde is needed. To gain insight into the problem, several routes to aldehydes have been examined.

To initiate the study, α-acetoxyisobutyraldehyde (154) was chosen for substrate 143. Employing a reaction developed by Corey and Seebach,[84] acetone was condensed with the lithium derivative 155 of 1,3-dithiane. Isopropenyl acetate, in the presence of *p*-toluenesulphonic acid, smoothly converted the resulting alcohol 156 to its acetate (157). The least satisfactory step in the synthesis was the hydrolysis of the thioacetal. Numerous meth-



ods[85,86,87] were available to accomplish this process. Of these, mercuric chloride and cadmium carbonate promised exceptionally mild hydrolytic conditions. With these two reagents, improved yields for hydrolysis have been reported by substituting acetonitrile or methanol for acetone, the usual solvent.[87] However because we suspected that the volatility of 154 might make work-up awkward, the hydrolysis of 157 was attempted using the lower-boiling acetone as solvent. Even so, the volatility of 154 complicated and prolonged its isolation. Nevertheless, extended heating of a mixture of 157, mercuric chloride, and freshly prepared cadmium carbonate afforded the desired product in *ca.* 40% yield. An appreciable amount of starting material was recovered and some decomposition of the aldehyde had apparently occurred during the long reaction time and work-up. For the preparation of an aldehyde group in a nonvolatile methynolide precursor, this complication may be reduced by using acetonitrile as solvent. Certainly the work-up procedure would be much more straightforward.

A second aldehyde synthesis was next examined, based on more traditional reactions. This work was directed towards the more manageable aldehyde 159. The acetylation

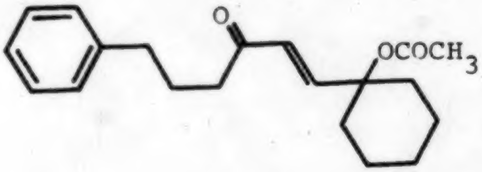


158 153 159

of 1-vinylcyclohexanol, obtained in good yield from the Grignard reaction of cyclohexanone and vinylmagnesium chloride,[88] proved troublesome. A procedure analogous to the acetylation of 156 gave the desired acetate 153 in 50% yield along with one major and one minor by-product (*ca.* 20-30% total impurity). The nmr spectrum of the main by-product suggested a mixture of diene isomers. Acetylation of the lithium salt of 158 with either acetyl chloride or acetic anhydride was incomplete and 153 was accompanied by dienic products. However satisfactory results were obtained when 1-vinylcyclohexanol was added sufficiently slowly to a heated, dilute solution (0.002-0.003 *M*) of *p*-

toluenesulphonic acid in isopropenyl acetate so as to maintain low concentrations (0.08-0.008 M) of alcohol in the reaction mixture. The product, isolated in 83% yield, contained less than 5% of the starting material and by-products. Ozonolysis of 153, followed by reduction with dimethylsulphide,[89] gave 159 in 33% yield.

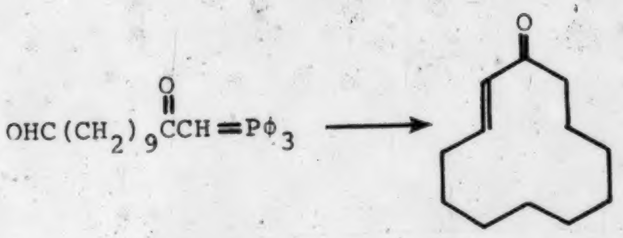
The Wittig reaction of 145 and 159 proceeded at a convenient rate at 90-100°. The desired product (160) was isolated in 71% yield. As expected, the nmr spectrum



160

of 160 showed no evidence of the *cis* isomer. It was gratifying to find that apparently little of the aldehyde decomposed during the reaction.

With this initial encouragement, we next wished to assess the practicality of using an intramolecular Wittig reaction to generate medium rings. The simplest test reaction is shown below. The generation of 161 would have to be carried out at high dilution to minimize intermolecular processes. Two independent syntheses of 161 are reported here. The prime difference between the two routes is the manner in which the aldehyde moiety was



161 162

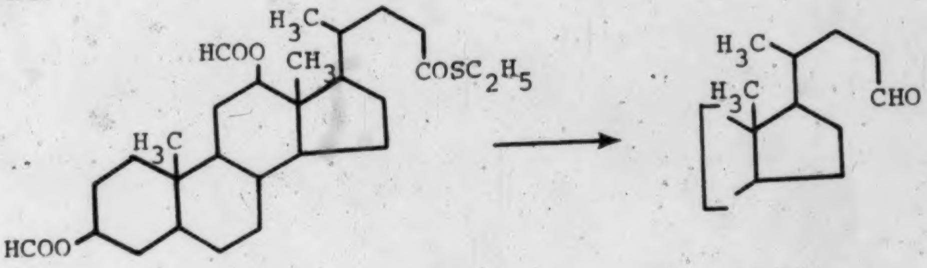
formed. Both reactions, reduction of a thiol ester with deactivated Raney nickel and Collins' oxidation of a primary alcohol, are essentially neutral.

Route 1

In 1946 Wolfrom and Karabinos[90] reported that thiol esters could be reduced successfully to aldehydes by refluxing the ester in aqueous ethanol in the presence of W-2 Raney nickel (prepared by Mozingo's procedure[91]).

$$R\overset{O}{\overset{\parallel}{C}}SR' + Ra\text{-}Ni(H_2) \longrightarrow RCHO + R'H$$

Wolfrom developed the reaction with the intent to provide an alternative method for preparing aldehydo carbohydrates, normally synthesized by the hydrolysis of the corresponding thioacetals. Although only modest yields of aldehydo sugars were obtained, the reduction gave good results with simpler substrates. Later work by Spero *et al.*[92] showed that Wolfrom's procedure often led to only trace amounts of aldehydes because of over-reduction to alcohols. They were able to circumvent this problem by first deactivating the catalyst in boiling acetone. With this modification a good conversion of **163** to diformoxycholanal (**164**) was realized. Very little use has since been made of this reaction.



163 **164**

Of interest to us however was a report by Bestmann and coworkers[93] in 1966, in which they announced a new bishomologation sequence. When S-ethyl dodecanethioate (**165**) was reduced with W-1 Raney nickel (not previously deactivated) in the presence of carbomethoxymethylenetriphenylphosphorane (**166**), the generated aldehyde was trapped as **167** by a Wittig condensation.* Subsequent hydrogenation and saponification gave a 65% overall yield of tetradecanoic acid. By analogy, **168** was chosen as the starting material for the model cyclization experiment.

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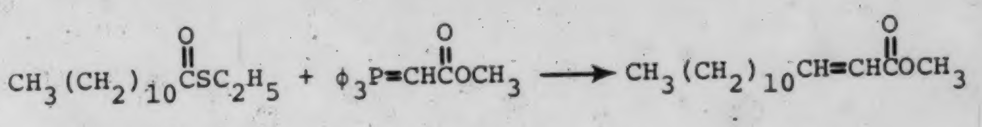
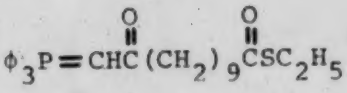
*Partial hydrogenation of the new double bond also occurred.



$$CH_3(CH_2)_{10}\overset{O}{\overset{\|}{C}}SC_2H_5 + \phi_3P{=}CH\overset{O}{\overset{\|}{C}}OCH_3 \longrightarrow CH_3(CH_2)_{10}CH{=}CH\overset{O}{\overset{\|}{C}}OCH_3$$

165 **166** **167**

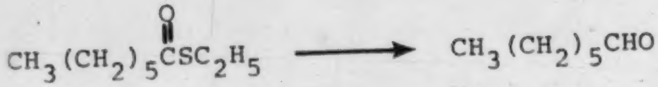


$$\phi_3P{=}CH\overset{O}{\overset{\|}{C}}(CH_2)_9\overset{O}{\overset{\|}{C}}SC_2H_5$$

168

Before attempting the synthesis of **168**, some simple experiments were performed to establish reaction conditions and to gain experience with Raney nickel catalysts. We found that S-ethyl heptanethioate (**169**) in 20% aqueous dioxane at 60° was smoothly and cleanly converted to heptanal (75% yield) by partially deactivated W-1 Raney nickel. Extended reaction times gave lower yields of the aldehyde and small amounts of heptanol. In anhydrous solvent the yield of heptanal dramatically dropped to 35%. At a reaction temperature of 90°, over-reduction became a problem. We also observed that the rate of reduction was not reproducible from one batch of catalyst to another. However the yield of heptanal was.

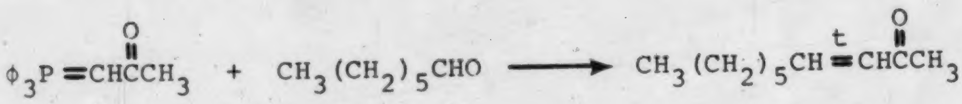
It was likely that the acylmethylenetriphenylphosphorane group of **168** would be stable to warm (60°) aqueous dioxane. To hydrolyse such a phosphorane normally



$$CH_3(CH_2)_5\overset{O}{\overset{\|}{C}}SC_2H_5 \longrightarrow CH_3(CH_2)_5CHO$$

169 **170**

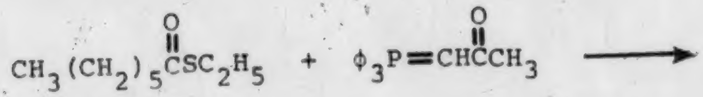
boiling aqueous alkali is needed. Nevertheless, the possibility was examined by heating at 60° a 20% aqueous dioxane solution containing acetylmethylenetriphenylphosphorane (**171**) and an excess of heptanal. The low initial



$$\phi_3P{=}CH\overset{O}{\overset{\|}{C}}CH_3 + CH_3(CH_2)_5CHO \longrightarrow CH_3(CH_2)_5CH\overset{t}{=}CH\overset{O}{\overset{\|}{C}}CH_3$$

171 **170** **172**

concentrations of reactants caused the complete reaction of **171** to require approximately 20 hours. Glpc analysis (UCW-98) indicated that *trans*-2-oxo-3-decene (**172**) was formed in 90% yield. The *trans* configuration of the double bond was concluded on the basis of the nmr spectrum of the product. The preparation of **171** had been reported previously.[94] As a follow-up experiment an aqueous dioxane solution of equimolar quantities of **171** and the thiol ester **169** was treated with partially deactivated W-1 Raney nickel at 60°. After five hours the solution was filtered from the catalyst and then heated to reflux. The yield of **172** was *ca.* 50%. Not all of the heptanal formed reacted



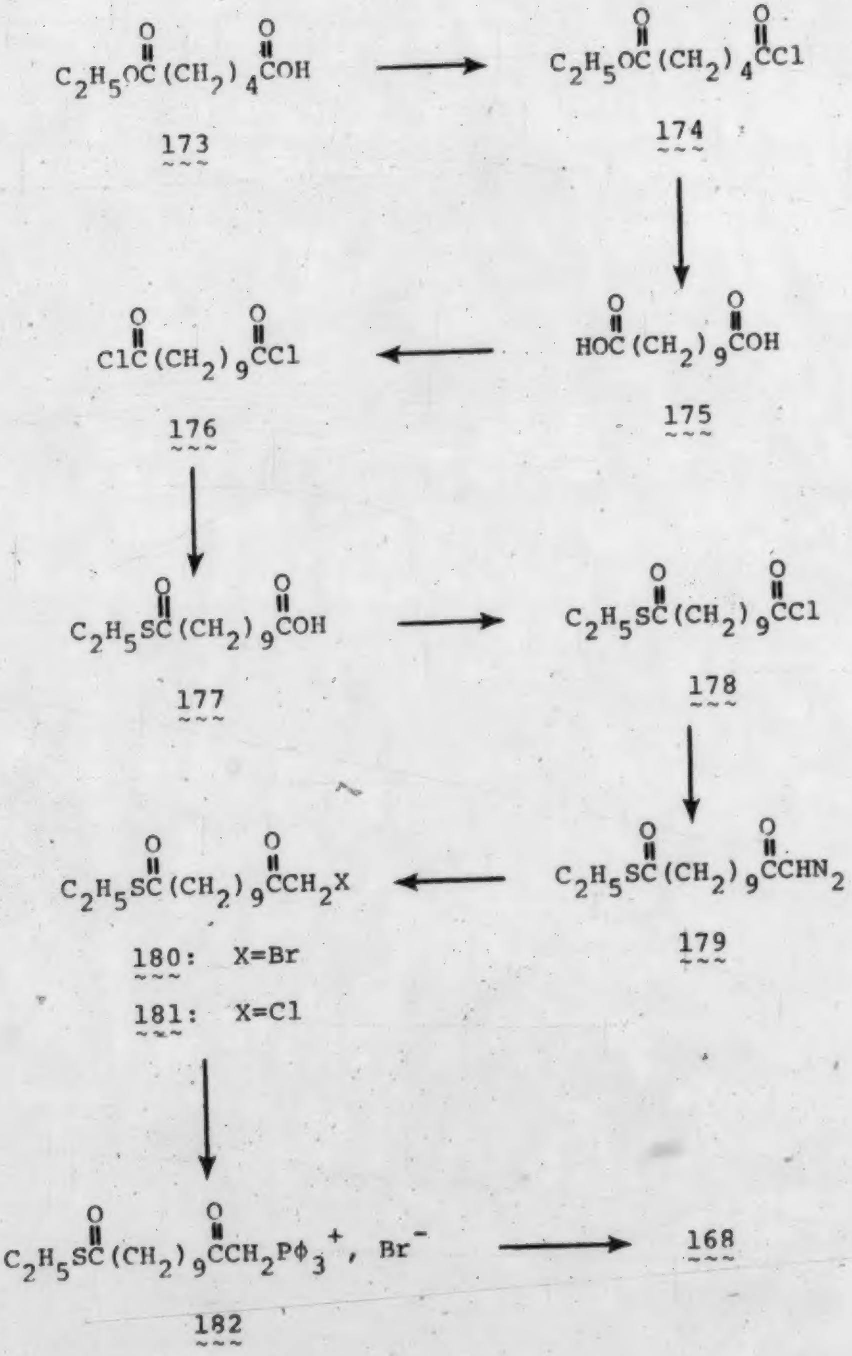
$$CH_3(CH_2)_5\overset{O}{\overset{\|}{C}}SC_2H_5 + \phi_3P{=}CH\overset{O}{\overset{\|}{C}}CH_3 \longrightarrow 172$$

169 171

even after extended heating. This can be explained if the surface of the nickel catalyst had been somewhat basic (*i.e.* basic enough to have caused partial hydrolysis of 171). On the whole though, we were encouraged by these findings to proceed with the synthesis of 168.

The sequence of chemical reactions, which is summarized in Scheme 6, led to the desired compound without difficulty. Ethyl hydrogen adipate (173), prepared from adipic acid, was converted to its acid chloride 174 which was in turn transformed, following reported procedures,[95] into undecanedioic acid (175). Treatment of the diacid chloride 176 with one mole equivalent of ethanethiol gave, after aqueous work-up and chromatography, 177 in 32% yield. By the same sequence of reactions used previously for the synthesis of 145, the carboxy group of 177 was transformed via the acid chloride and the diazoketone into 180. The nmr spectrum of 180 suggested the presence of approximately 6% of the α-chloromethyl ketone 181. Reaction of the bromo ketone with triphenylphosphine in benzene and chromatography of the crude product on

Scheme 6



$C_2H_5O\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}OH$ 173 $\longrightarrow$ $C_2H_5O\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}Cl$ 174

$\longrightarrow$ $HO\overset{O}{\overset{\|}{C}}(CH_2)_9\overset{O}{\overset{\|}{C}}OH$ 175 $\longrightarrow$ $Cl\overset{O}{\overset{\|}{C}}(CH_2)_9\overset{O}{\overset{\|}{C}}Cl$ 176

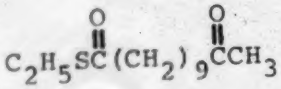
$\longrightarrow$ $C_2H_5S\overset{O}{\overset{\|}{C}}(CH_2)_9\overset{O}{\overset{\|}{C}}OH$ 177 $\longrightarrow$ $C_2H_5S\overset{O}{\overset{\|}{C}}(CH_2)_9\overset{O}{\overset{\|}{C}}Cl$ 178

$\longrightarrow$ $C_2H_5S\overset{O}{\overset{\|}{C}}(CH_2)_9\overset{O}{\overset{\|}{C}}CHN_2$ 179 $\longrightarrow$ $C_2H_5S\overset{O}{\overset{\|}{C}}(CH_2)_9\overset{O}{\overset{\|}{C}}CH_2X$

180: X=Br

181: X=Cl

$\longrightarrow$ $C_2H_5S\overset{O}{\overset{\|}{C}}(CH_2)_9\overset{O}{\overset{\|}{C}}CH_2P\phi_3^+,\ Br^-$ 182 $\longrightarrow$ 168 silicic acid gave pure phosphonium bromide **182**. The overall yield from **177** to **182** was 66%. A small amount of a second compound was isolated during the chromatography of **182**. On the basis of its nmr and ir spectra, structure **183** is assigned to the by-product. The nmr spectrum ($CDCl_3$)



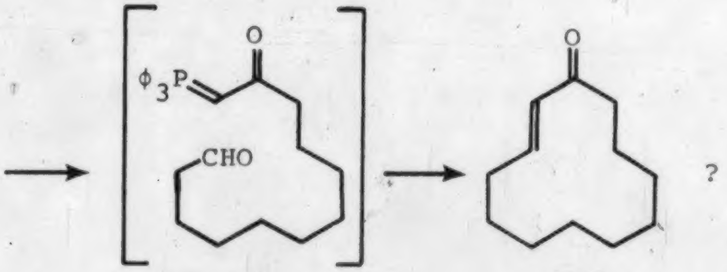
$$C_2H_5S\overset{O}{\overset{\|}{C}}(CH_2)_9\overset{O}{\overset{\|}{C}}CH_3$$

183

shows the absence of aromatic protons, the presence of the S-ethyl thioate group, and a singlet at τ 7.87. Integration is consistent with **183**. The ir spectrum ($CHCl_3$) contains two carbonyl stretching absorptions at 1707 cm^{-1} and 1678 cm^{-1}, attributable to the methyl ketone and to the thiol ester respectively. In addition there is a medium absorption at 1355 cm^{-1} which is absent in both **180** and **182**. The wavenumber agrees well with that expected for the characteristic CH_3 deformation band of methyl ketones. Since **183** was present in the crude phosphonium bromide before chromatography, it is not clear to us how **183** was formed. Removal of the acidic proton in **182** was accomplished by adding one equivalent of _n_-butyllithium to a benzene solution of **182**. A mercaptan smell was detected during the reaction, suggesting that the thiol ester group had been partially destroyed by local, high concentrations of n-butyllithium formed during the addition of the base. The nmr spectrum ($CDCl_3$) of the crude phosphorane 168 showed a small, distorted and poorly defined triplet in the region τ 9.0-9.2. This region was clear in the nmr spectra of 180 and 182. The maximum amount of n-butyl-containing impurity in 168 was estimated as 20%. Crystallization of 168 could not be induced; further attempts to purify the compound were not pursued.

The cyclization experiment was carried out in the following manner. The activity of a fresh batch of W-1 Raney nickel was standardized using S-ethyl heptanethioate (169). Thus a 0.01 M solution of 169 in 20% aqueous dioxane was reduced with partially deactivated Raney nickel to heptanal in 75% yield after five hours stirring at 60°. A 0.0067 M solution of impure 168 in 20% aqueous dioxane, containing cyclododecane as an internal glpc standard, was then similarly treated with partially deactivated catalyst at 60° for five hours. The reduced solution was cooled, the catalyst was removed by filtration, and the filtrate was diluted with roughly an equal volume of heptane. The solution (ca. 0.0028 M in phosphorus compounds) was dried briefly with anhydrous sodium sulphate and heated at reflux for several days. After work-up the glpc trace (UCW-98) of the reaction mixture contained five main peaks with retention times equal to or longer than that of cyclododecane. By glpc-mass spectral analysis one of the peaks corresponded to a compound having an apparent parent ion at *m/e* 180. Authentic *trans*-2-cyclododecenone has an evident parent ion (P) at *m/e* 180 (*vide infra*).

168



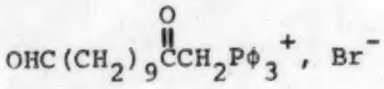
161

162

Although admittedly this represents very tenuous evidence of cyclododecenone, we decided not to extend this work for several reasons. Firstly, the yield of the presumed cyclododecenone was only *ca*. 3-5%. We felt that the low yield might be largely due to the nature of the Raney nickel reduction. Under the best circumstances, the yields of aldehydes are only 75%. Because it is impossible to follow the progress of the reduction of **168**, it is necessary to assume that **168** and the simple thiol ester **169** behave identically. This may not be so. In addition, the nickel catalyst may be partially hydrolysing the phosphorane group. The synthesis of **161** was consequently approached from another direction. By the second route encouraging yields of cyclododecenone were realized.

Route 2

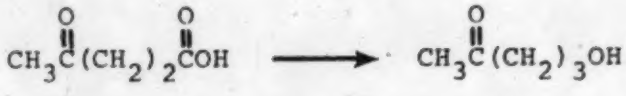
It is obviously desirable to produce **161** from its immediate precursor in guaranteed high yield. To avoid unnecessary intermolecular condensations of **161**, such a reaction should be practical in highly dilute solutions. These conditions are fulfilled by generating the aldehyde at an earlier stage in the synthesis and by then relying upon the titration of **184** with one equivalent of base to set up the molecule for an intramolecular Wittig reaction.



$$\mathrm{OHC(CH_2)_9}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{CH_2P\phi_3}^{+}\mathrm{,\ Br^-}$$

184

Scheme 7 outlines the transformations that were performed in order to accomplish the synthesis of **184**.

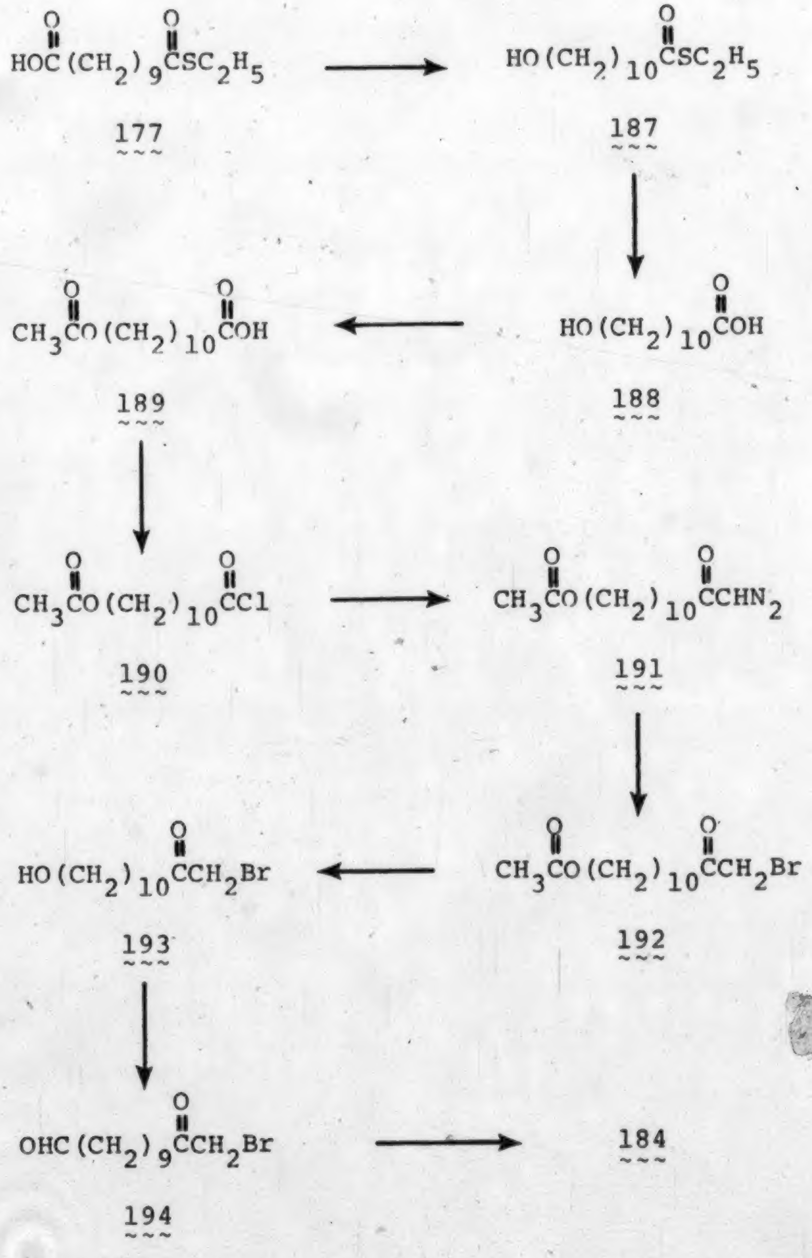


$$\mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{(CH_2)_2}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{OH} \longrightarrow \mathrm{CH_3}\overset{\mathrm{O}}{\overset{\|}{\mathrm{C}}}\mathrm{(CH_2)_3OH}$$

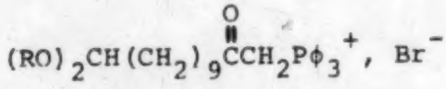
185 **186**

Rao and Thakar[96] had observed that a solution of borane in tetrahydrofuran selectively reduced the carboxy group of **185**. They isolated 5-hydroxy-2-pentanone in 64% yield. We observed a similar preference for borane to reduce the carboxy group of **177**. A 73% yield of pure S-ethyl 11-hydroxyundecanethioate (**187**) was obtained. Saponification and acetylation converted **187** into a mixture of **189** and the corresponding mixed anhydride. Hydrolysis of the mixture in hot aqueous tetrahydrofuran, followed by chromatography on silicic acid afforded pure **189** (82% yield from **187**). The bromomethyl ketone **192** was prepared by the usual series of reactions. Again a small amount (*ca*. 10%) of the chloro derivative was also formed. Removal of the acetyl protecting group was accomplished by refluxing **192** in dry methanol containing a trace of *p*-toluenesulphonic acid. Chromium trioxide-pyridine complex, dissolved in methylene chloride,[97] cleanly oxidized **193** to the desired aldehyde **194** in less than two minutes and in greater than 90% yield. Longer reaction times had a deleterious effect on the bromo ketone moiety. Although the nmr spectrum of the aldehyde was excellent, tlc analysis (silica gel) indicated a small amount of impurity. Chromatography of **194** on silicic acid, eluting with a mixture of chloroform and carbon tetrachloride, removed the original impurity but tlc of the eluted product showed that a small amount of a new substance had formed, presumably the diethyl

Scheme 7


HOC(CH2)9CSC2H5
177
HO(CH2)10CSC2H5
187
HO(CH2)10COH
188
CH3CO(CH2)10COH
189
CH3CO(CH2)10CCl
190
CH3CO(CH2)10CCHN2
191
CH3CO(CH2)10CCH2Br
192
HO(CH2)10CCH2Br
193
OHC(CH2)9CCH2Br
194
184

acetal of **194** (*vide infra*). With benzene--ethyl acetate as eluent in the chromatography of **194**, no complication arose. Finally, the phosphonium salt **184** was prepared by refluxing **194** and a small excess of triphenylphosphine in benzene. To remove the unreacted phosphine, the crude salt was applied to a silicic acid column and eluted with chloroform containing 3% methanol. Greater than 50% of **184** was transformed into a new substance(s), which moved on tlc (silica gel) with a larger R_f value. The nmr spectrum ($CDCl_3$) gave strong evidence for the presence of **184**, **195**, and **196**. A sharp singlet at τ 6.68, characteristic



$$(RO)_2CH(CH_2)_9\overset{O}{\overset{\|}{C}}CH_2P\phi_3^+,\ Br^-$$

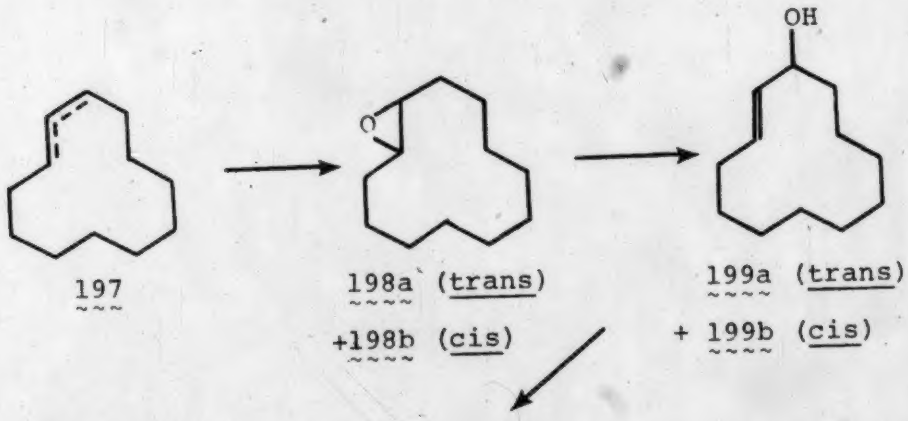
195: $R{=}CH_3$

196: $R{=}C_2H_5$

of a methyl ether, and an ill-defined absorption at τ 5.60, consistent with the methine proton of an acetal, were observed. In addition, an absorption with complex splitting was seen at τ 6.2-6.6. Both the chemical shift and the complexity of the splitting suggested that the diethyl acetal **196** was also present. The aldehyde could be regenerated by heating the mixture in aqueous mineral acid. In later preparations of **184**, the crude phosphonium bromide was used directly to prepare the phosphorane. We felt that the presence of unreacted triphenylphosphine would not likely interfere with the Wittig condensation.

The cyclization experiment was conducted in the following way. To generate the desired phosphorane **161**, a dilute methanolic toluene solution of **184** (approximately 0.002 *M*) was treated at -78° with 0.8 mole equivalent (based on **194**) of methanolic sodium methoxide. After warming to room temperature, the mixture was further diluted with toluene. The majority of the methanol was then removed by distilling a small portion of the solvent through a spinning-band column. In Experiment 1, the reaction mixture was refluxed under nitrogen for 100 hours. The approximate concentration of the phosphorane was 0.0013 *M*. Experiment 2 was conducted under somewhat different conditions. After removal of the methanol, the solution was degassed and sealed in a Carius tube, which was then heated at 200° for 100 hours. In this reaction the phosphorane concentration was about 0.00029 *M*. Following the heating period, each solution was concentrated carefully by spinning-band distillation during which constant glpc monitoring of the distillate showed no evidence of products. A known quantity of tetradecane was then added to the concentrates to serve as an internal glpc standard.

For the purpose of analytical evaluation of the reaction products, authentic *trans*-2-cyclododecenone (**162**) was prepared, starting from an isomeric mixture of cyclododecenes (**197**). The conversion of the epoxides **198a**,**b** into *cis*- and *trans*-2-cyclododecenone and the isolation of the latter had been reported previously.[98]



197

198a (*trans*)
+**198b** (*cis*)

199a (*trans*)
+ **199b** (*cis*)

162
+ *cis*-2-cyclododecenone

A glpc-mass spectral analysis (Carbowax 20m) of the cyclization concentrates revealed three different compounds, **A**, **B**, and **C**, with likely parent ions (P) at *m/e* 180. All three spectra were very similar, differing only slightly in the relative intensities of fragment ions. Furthermore, **162** and **C**, the isomer with the longest glpc retention time, had identical mass spectra and identical retention times on various glpc systems (UCW-98, Carbowax 20m, and Reoplex). On the basis that **A**, **B**, and **C** are isomeric cyclododecenones*, the yields of the cyclized products are summarized in Table 2. For quantitative analysis it was assumed that isomers **A** and **B** exhibit the same glpc response relative to tetradecane as does **162**. Evidence cited above suggests that **C** and **162** are one and the same.

Two results of the cyclization experiments deserve comment. Most important are the relatively good total yields of cyclododecenones. Secondly, in Experiment 1 (conducted at 100°), *trans*-2-cyclododecenone, the expected isomer from the Wittig reaction, was the major product. In contrast, at the higher temperature employed in Experiment 2, the results indicate that the initially formed **162** isomerized extensively. At the expense of **162** the yield of **A** tripled and that of **B** increased about nine fold. The relative amounts of ring strain in the various cyclododecenone isomers undoubtedly plays an important role in determining the proportion of each isomer under equilibrating conditions at a particular temperature.

Further evidence was necessary that **A**, **B**, and **C** are isomeric cyclododecenones. Since the total amounts of cyclododecenones in the reaction concentrates were very

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*The isomeric purity of each of the three glpc peaks is not known.

Table 2: The Cyclization of 161

Exp.	Concn. (M)	Temp. (°)	Cyclododecenones (% Yield)[a]				Cyclododedecanone (% Yield)[a]
			A (-3.9)[b]	B (-2.8)[b]	C (=162)	Total	(ca. -5.2)[b]
1	0.0013	100	7.9	1.2	23	32	
2	0.00029	200	24	9.0	8.7	42	
(1,H_2)							20
(2,H_2)							28
3			12	0	88		
4	0.0012	110	15	0	75		
5	0.0012	210	13	31	44		

a) The product yields were calculated with reference to standard solutions of trans-2-cyclododecenone and cyclododecanone.

b) The value represents the relative retention time (min) with respect to 162. Glpc analysis was conducted using a 6 ft Carbowax 20m column programmed as follows: (1) 80°, 4 min, (2) +4°/min to 180°, and (3) isothermal at 180°.

small (*ca*. 1.8 mg for Experiment 1 and 0.84 mg for Experiment 2), direct isolation of the products was not possible. As a second-best solution, each concentrate was hydrogenated over a palladium-carbon catalyst under one atmosphere of hydrogen. The glpc traces of the reduced solutions showed no evidence of compounds **A**, **B**, or **C**. In their place a new substance had appeared. The new product and authentic cyclododecanone had identical mass spectra and identical retention times on various glpc systems (UCW-98, Carbowax 20m, and Reoplex). The calculated yields of cyclododecanone account for about 65% of the total yields of cyclododecenones. The results are tabulated as Experiment (1,H_2) and Experiment (2,H_2) in Table 2. The correlation between the yields of the enones and the yields of the saturated ketone is strong enough to conclude that **A** and **C** (**162**) are indeed isomers.

In another series of experiments the thermal stability of *trans*-2-cyclododecenone was examined. Concerning this subject, it had been noticed earlier in this work that the purity of **162** deteriorated at room temperature. An impurity appeared having the same glpc retention characteristics (Carbowax 20m) as **A**. The mass spectrum (likely P at *m/e* 180) of the impurity strongly resembled those of **A**, **B**, and **162**. (There were some differences in the relative intensities of corresponding ions in the spectra of the impurity and **A**, suggesting either that they may be isomeric or that one of them may be a mixture of isomers. For simplicity of argument, the two will be considered as identical.) Two identical toluene solutions of **162**, containing some triphenylphosphine and triphenylphosphonium oxide, were heated at 110° and 210°. After 80 hours the solutions were analysed by glpc. The results are summarized as Experiments 4 and 5 in Table 2. The sample of **162** used in these runs contained some isomer **A**. The composition of the impure **162** is recorded as Experiment 3 in Table 2.

Qualitatively the results of Experiments 4 and 5 are in line with those of Experiments 1 and 2. At 100-110°, the reaction products of both Experiments 1 and 4 contained only traces of **B**. However at 210°, significant isomerization of **162** to a substance with a similar glpc retention time as **B**, is observed (Experiment 5). A parallel change is seen when Experiments 1 and 2 are compared. These findings constitute further support that **162** and **B** are isomeric. Surprisingly, the content of **A** remained unchanged in Experiments 4 and 5. This may result from differences in the reaction conditions between the cyclization runs and the isomerization runs.

The results of Experiments 4 and 5 were reproduced when 162 was isomerized in the absence of phosphorus compounds.

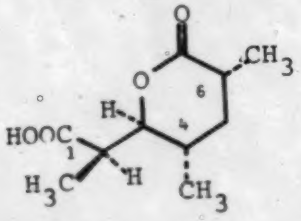
It should be mentioned that in these studies toluene proved to be a poor choice of solvent. All reaction mixtures were contaminated by varying amounts of benzyl alcohol, benzaldehyde, and 1,2-diphenylethane.

Based on the experimental findings presented in this chapter, we concluded that Type B ring closure deserves serious consideration in our synthesis of methynolide.

CHAPTER 7

A SYNTHESIS OF RACEMIC DJERASSI-PRELOG LACTONIC ACID

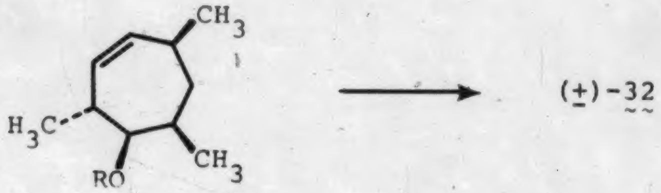
An effective synthesis of the Djerassi-Prelog lactonic acid (±)-32 necessitates that the four asymmetric



(±)-32

centres be introduced in a relatively high stereoselective manner. Otherwise, the overall yield may be impractically low and experimental difficulties may arise concerning the separation and identification of diastereoisomers. In the preparation of the four lactonic acids 113a-d, mentioned earlier in Chapter 4, the Russian workers had to contend with these problems.

The art of stereoselective generation of asymmetric centres in a flexible acyclic carbon chain is still in infancy. It was reasonable then to simplify our task as much as possible by introducing the asymmetry into cyclic structures. Later cleavage of the ring(s) would give suitable precursors of (±)-32. Accordingly, the trimethylcycloheptenol derivative **200** was selected as the key synthetic intermediate. Oxidative cleavage of the double bond, followed by removal of the hydroxy-protecting

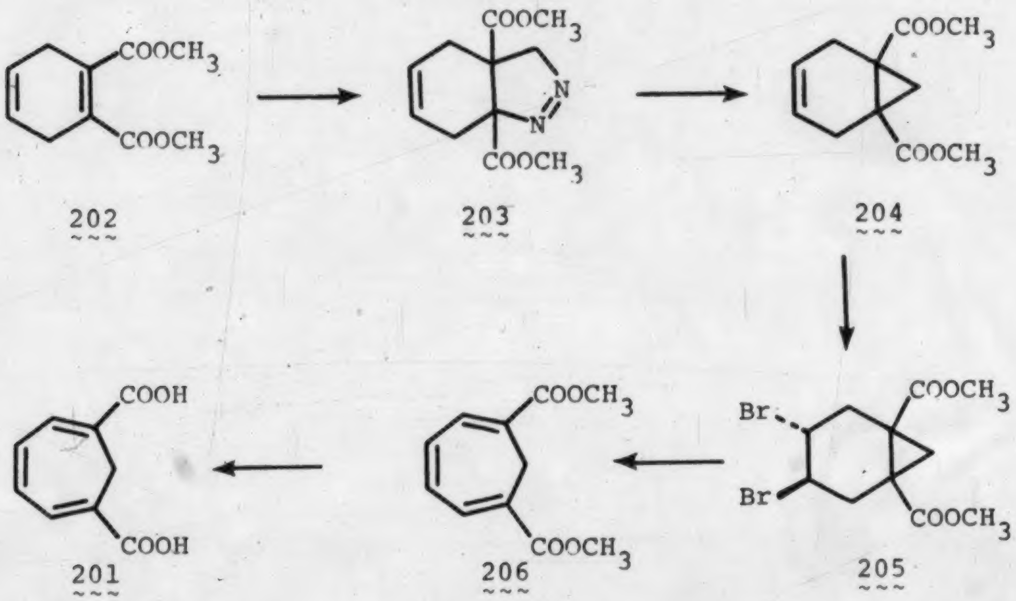


200

group, should then lead directly to (±)-**32**.

The starting material for the synthesis of **200** was 3,5,7-cycloheptatriene-1,3-dicarboxylic acid (**201**). The compound had been previously prepared by two research groups.[99] The more recent route of Vogel and coworkers[99b] held distinct advantages and was adopted by us. The specific steps are illustrated in Scheme 8 to help point out some disadvantages of this method for large-scale preparations. In the first place, addition of diazomethane to the Diels-Alder product **202** to give **203** is not very efficient. In order to obtain high conversions (>80%) to the pyrazoline in large-scale reactions, it was found necessary to work-up the mixture at four- to six-day intervals and then add fresh diazomethane solution. At least three treatments with diazomethane were required. Often the solutions contained as much as one mole of diazomethane.

Scheme 8


COOCH3
COOCH3
202
COOCH3
N
N
COOCH3
203
COOCH3
COOCH3
204
Br
Br
COOCH3
COOCH3
205
COOCH3
COOCH3
206
COOH
COOH
201

The second serious limitation involves the photolytic decomposition of the pyrazoline to **204**. The photolysis proceeded in high yield, only however when relatively small amounts (<5 g) of pyrazoline were used. With larger portions of **203**, significant amounts of by-products formed. The impurities were troublesome to remove.

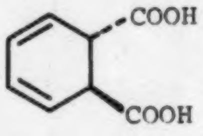
We planned the ultimate fate of the carboxy groups of **201** to be the two methyl groups at C_4 and C_6 in (±)-**32**. Consequently a cis orientation of the carboxy groups had to be developed from **201**.

It has been known for some time that amalgamated metals of high oxidation potential can reduce a conjugated polyene chain, which contains unreactive, electrondelocalizing groups at each end. For instance both sodium amalgam and aluminum amalgam reduce the 1,6-diphenylhexatriene 207 in 60% yield to the 1,6-dihydro product 208.[100] In a similar example, phthalic acid is reduced by sodium

$$\phi CH{=}CH{-}CH{=}CH{-}CH{=}CH\phi \longrightarrow \phi CH_2CH{=}CH{-}CH{=}CHCH_2\phi$$

207 208

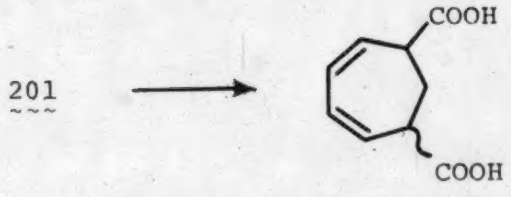
amalgam to *trans*-1,2-dihydrophthalic acid (209).[101] This reaction proceeds in yields up to 85%.[102]



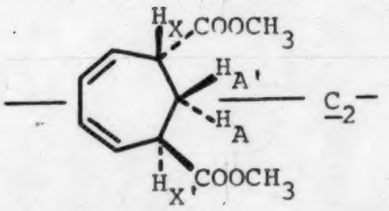
209

When an aqueous, buffered solution of the disodium salt of 201 was treated with an excess of 3% sodium amalgam, reduction took place exclusively at C_1 and C_3. By carefully controlling the pH of the reaction at *ca*. 8.0, 210 was obtained in quantitative yield. Analysis of the nmr spectrum (100.1 MHz, $CDCl_3$) of the dimethyl ester (211) of 210, prepared using diazomethane, permitted an accurate evaluation of the relative amounts of *cis* and *trans* products present.

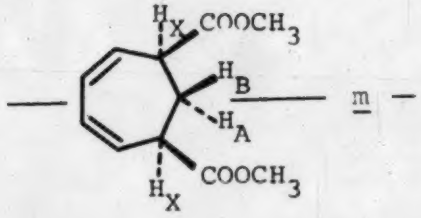
In the *trans* diester 212, the existence of a



210



212



213

two-fold rotation axis ($\underline{C}_2$) through the methylene group necessitates the chemical equivalence of the geminal protons on C_2. The methylene protons may be analysed as the AA' part of an AA'XX' nuclear spin system. This is only so because the chemical shift of the olefinic protons is well separated from the region of interest. In the general case, the AA' half of an AA'XX' spectrum consists of twelve lines.[103] For **212** it is reasonable to expect that $J_{X,X'} \approx 0$ Hz. Then the AA' pattern of the spectrum reduces to six lines. The experimental observation is a triplet (τ 7.75, J=6 Hz) which further demands that the *cis* and the *trans* coupling constants are equal (*i*.*e*.

$J_{A,X}=J_{A,X'}=6$ Hz).

In contrast to 212, the *cis* diester 213 has a mirror plane (*m*) through C_2 and no two-fold rotation axis. Consequently the two geminal protons on C_2 are not chemically equivalent. The two protons that are labelled H_A and H_B in 213 may be treated as the AB part of an ABX_2 spin system. The nmr spectrum of the second diester isomer exhibits a methylene pattern consisting of 12 lines. This is in line with what would be expected for an ABX_2 system but is incompatible with the AA'XX' nuclear system. Therefore this diester must be the *cis* isomer. The 12 lines appear as four, off-centre triplets (see Figure 7). The indicated values for the coupling constants $J_{A,X}$ and $J_{B,X}$ are only approximate since the spectrum is not first order.* Assignment of the two separated, low-field trip-

Figure 7

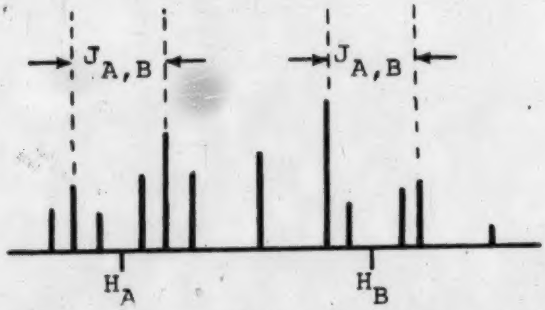
$\tau\ H_A = 7.47$

$\tau\ H_b = 7.82$

$J_{A,B} = 13.5$ Hz

$J_{A,X} \simeq 3.6$ Hz

$J_{B,X} \simeq 11.0$ Hz



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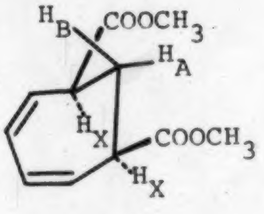
*From the chemical shifts and J values for protons H_A, H_B and H_X listed in Figure 7, computer calculations based on lets to H_A is based on two pieces of evidence. Molecular



213-A

models suggest that 213-A, in which the carbomethoxy groups are "equatorially" disposed, is the favoured conformation of the cis diester. In this conformation the dihedral angles between H_B and H_X and between H_A and H_X are roughly 170° and 80° respectively. Therefore according to the Karplus relation, $J_{B,X}$ should be larger than $J_{A,X}$. Secondly, the spectral representation in Figure 7 is really an over-simplification. Each of the six low-field lines is in fact further split into a doublet ($J \simeq 1$ Hz). The so-called zig-zag or W configuration of H_A and the olefinic protons at C_4 and C_7 supports the involvement of H_A rather than H_B in this long-range effect.*

The product (210) from the sodium amalgam reduction surprisingly contained 79% of the cis isomer 214.

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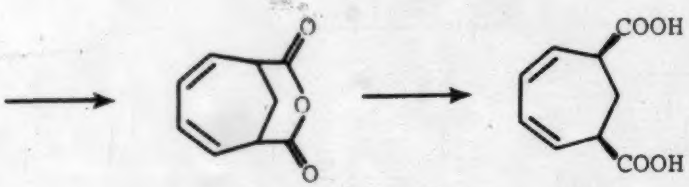
a general four spin system reproduce the observed methylene splitting pattern.

*Irradiation of the olefinic protons in the nmr spectrum of 213 removes this 1 Hz coupling.

Under epimerizing conditions, **213** is transformed (>95%) into **212**. In contrast, the reduction of phthalic acid leads exclusively to thermodynamically more stable *trans*-1,2-dihydrophthalic acid (**209**).

Only the *cis*-cycloheptadiene dicarboxylic acid was of use. When the mixture **210** was heated briefly in acetic anhydride, either alone or in the presence of pyridine, the cyclic anhydride **215** was formed in 80% yield. From **215** it was a simple matter to obtain **214**.

210

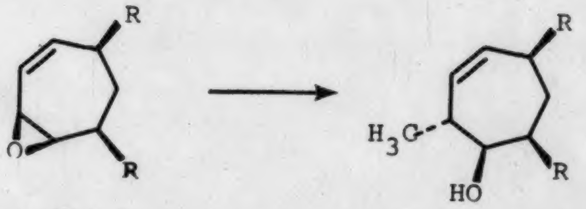


215

214

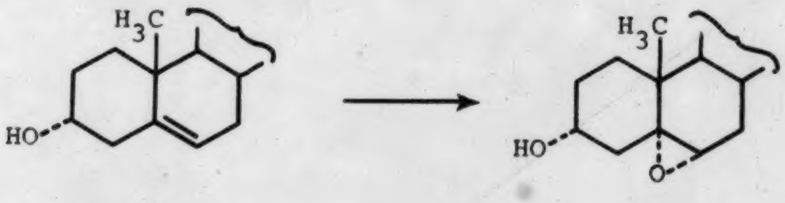
A critical stage had been reached towards the synthesis of **200**. Specifically one of the double bonds in **214** had to be difunctionalized. The most direct route to the *trans*-related hydroxyl and methyl groups (see **200**) is to open the monoepoxide of **214** (or a derivative thereof) with a methylating reagent. Only the epoxide that has the all-*cis* configuration (*i*.*e*. **216**) is useful in this approach.

Directing effects in epoxidation reactions are well known. Since 1957 when Henbest and Wilson[104] first announced that a cyclic olefin containing an allylic



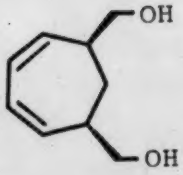
216 217

hydroxyl may be converted by organic peracids predominantly to the *cis* epoxide, the French research group led by Mousseron has demonstrated the generality of Henbest's findings for the preparations of a wide range of cyclic epoxides. In a dramatic example,[105] monoperphthalic acid converted 3-epicholesterol (218) almost exclusively into the α-epoxide. Only 5% of the product was the β-isomer. In contrast, the reagent attacked the acetate of 218



218 219

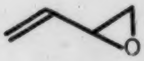
solely from the β-side. We were hopeful that a derivative of 214, such as 220, might also undergo mainly *cis* epoxidation. One advantage of 220 is its symmetry. Only two monoepoxides are possible. This should help simplify the interpretation of experimental results. As in 218, the



220

OH groups in 220 are homoallylic, however the latter have greater orientational freedom. The possible importance of this difference to the reaction mechanism was appreciated.

The alkylation of allylic epoxides has caught little attention. Recently however workers[106] have shown that both methylmagnesium chloride and dimethylmagnesium cleave the oxirane ring of 221 primarily by 1,2-addition.



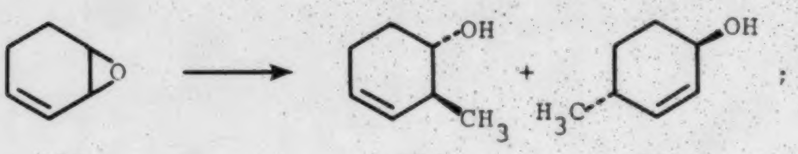
221

$Li^+ [Cu(CH_3)_2]^-$

222

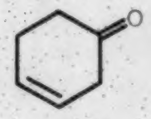
Appealing to us was lithium dimethylcuprate (222)[107] as a methylating reagent. Its low basicity would be advantageous if the R groups in 216 were susceptible to epimerization. The cuprate reagent is known to open oxiranes in good yield, with inversion at the newly alkylated carbon.[108] Unfortunately when 221 is the substrate, 94% of the crude product is derived from 1,4-addition.[106] However to assume on this information that 216 would also form the 1,4-product seemed to us unjustified. The accessibility of the terminal carbon of the double bond in 221 would be expected to favour 1,4-addition.

In order to assess more confidently the applicability of 222 to the reaction 216→217, we examined the products obtained when 3,4-epoxy-1-cyclohexene (223) is treated with 222. The alcohols 224 and 225 are obtained in roughly equal proportions with an overall yield of 85-90%. This study was performed by Dr. C. Kim. Shortly after the completion of this work, two research groups[109] reported results in agreement with ours. The only impurity in the product is 3-cyclohexen-1-one (226), occurring in variable amounts (0-23%). Staroscik and Rickborn also found that alkylation using dimethylmagnesium gives 224 as the sole product in 95% yield.[109a]



223 224 225

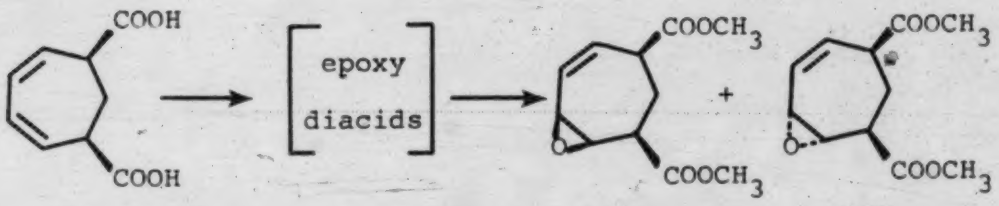
;



226

With knowledge of the behaviour of various methylating reagents on 223, we next directed efforts towards the synthesis of 216. The diol 220, prepared by the reduction of 215 with lithium aluminum hydride, was treated with one mole equivalent of *m*-chloroperbenzoic acid. The reaction product(s) proved to be difficult to analyse. Chromatography of the crude product and certain of its derivatives did not afford any identifiable compounds. Likely one factor contributing to the problem was the nature of the product. Monoepoxides of conjugated dienes are known to be sensitive compounds, particularly towards acids.[110]

The direct epoxidation of the cycloheptadiene dicarboxylic acid **214** was then examined. One mole equivalent of *m*-chloroperbenzoic acid reacted rather slowly with **214**. At room temperature, approximately 24 hours were required for the disappearance of 90% of the starting material. To aid in the interpretation of the nmr spectrum, the crude mixture was esterified using diazomethane. The nmr spectrum (CCl_4) of the esterified product was too complicated to analyse. Nevertheless the gross features are very informative. Besides the absorptions due to methyl *m*-chlorobenzoate, the spectrum con-



214 **227** **228**

tains a two-proton multiplet centred at τ 4.07, methylester peaks (six protons) at τ 6.15-6.34, a broad four-proton absorption at τ 6.30-7.20, and a two-proton multiplet centred at τ 7.80. The general appearance is therefore consistent with the structure of a monoepoxide. In fact both possible monoepoxides, **227** and **228**, are formed in nearly equal amounts. This conclusion was reached by examining an expansion of the region containing the methyl singlets (Figure 8). The large singlet at 381.0 Hz is due to the methyl group of the benzoate ester. At higher field there are two pairs of singlets in a *ca*. 60:40 ratio. The small amount of **213** present shows as a slight intensification of the peak at 359.5 Hz.

A mixture of methylene chloride and tetrahydrofuran was the solvent medium for the epoxidation. Attempts to increase the stereoselectivity of the reaction, either towards epoxide A or epoxide B, by varying the solvent system met with little success. With pure tetrahydrofuran the isomer ratio changes to 1:1. Although the epoxides were not further characterized, we felt quite confident that **227** was present in the product and we decided to continue with the synthesis.

When the crude epoxide mixture (**227** and **228**) was chromatographed on silicic acid to remove the methyl

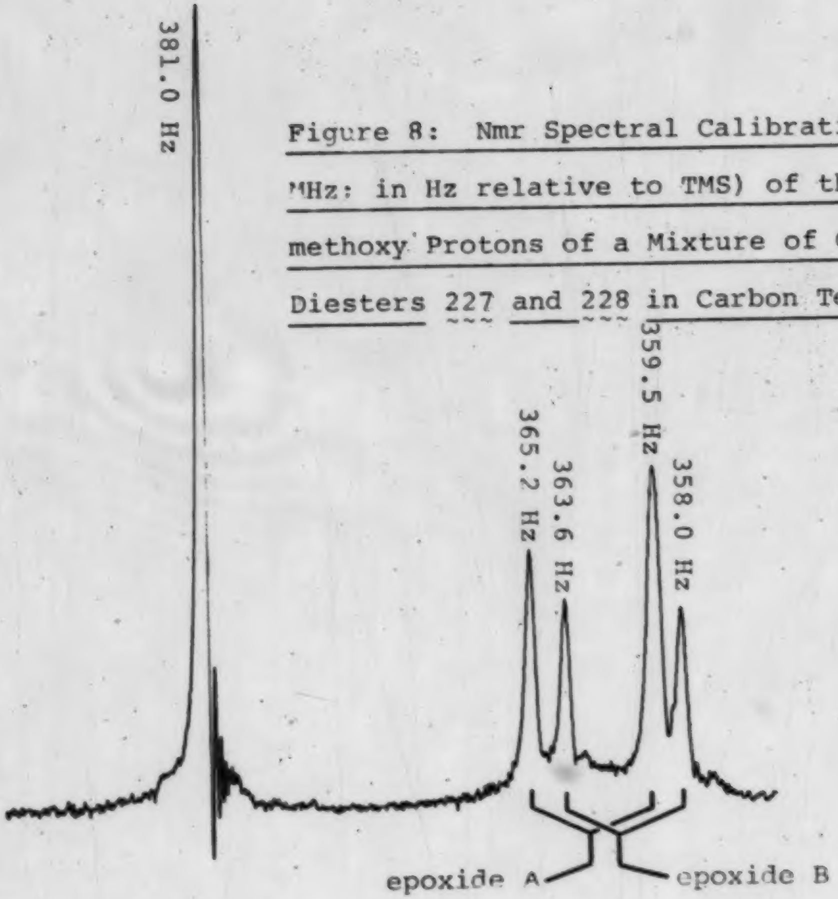
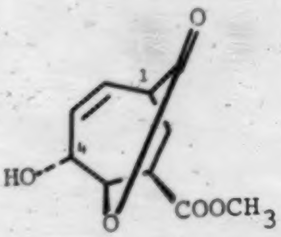


Figure 8: Nmr Spectral Calibration (100.1 MHz: in Hz relative to TMS) of the Carbomethoxy Protons of a Mixture of Crude Epoxy Diesters 227 and 228 in Carbon Tetrachloride

m-chlorobenzoate, approximately 25% of the product was transformed into a more polar substance. The ir spectrum of the new compounds exhibits a hydroxyl band (3640-3200 cm^{-1}) and a broad carbonyl band (1749 cm^{-1}). Coupled with an nmr analysis, the likely structure of the substance is shown below:



229

The assignment of the chemical shifts in the nmr spectrum of 229 is summarized in Table 3. Of particular importance in support of structure 229 are the isolated absorptions at τ 5.04 and τ 5.94. The position of the lower-field multiplet is quite similar to the C_5 proton of 233 (τ 5.22, see Table 4). There is no doubt about the structure of 233. The half-height width (60 MHz) of the two methine protons are also similar, 9 Hz in 229 and 7 Hz in 233. The half-height width of the broad doublet of doublets at τ 5.94 in 229 is 14 Hz. Furthermore, a chemical shift of τ 5.94 is characteristic of a methine proton geminal to the hydroxyl group in allylic alcohols. For instance, in compounds 199a,b the proton at C_1 appears as a broad

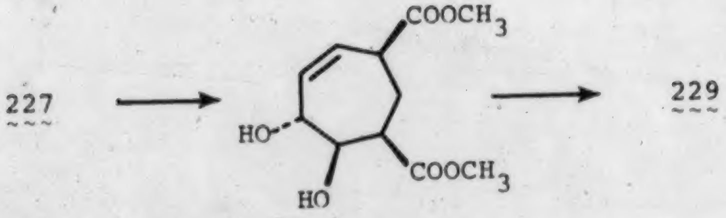
Table 3: Nmr Analysis (60 MHz, $CDCl_3$) of 229

Chemical Shift (τ) and Multiplicity[a] (Hz)					
$H_{2,3}$	H_5	H_4	CH_3	H_8	$H_{6,7A,7B}$
3.57	5.04	5.94	6.25	6.60	7.10-8.30
m	m	bd,9 d,2	s	bm	bm

a) For an explanation of the multiplicity abbreviations, see page 204, Chapter 10.

absorption at τ 5.96. Also from a mechanistic viewpoint, there is support for structure 229. Presumably the pathway to the lactone involves partial hydrolysis of the unstable allylic epoxide during the chromatography on silicic acid, followed by an internal transesterification. Hydrolysis of the *cis* epoxide 227 would be expected to give 230. Laconization leads directly to 229. In contrast, 228 would be expected to give 231 or 232.

Although lactone 229 was of no use to us, we were encouraged simply by its formation. The result suggested that if, in the place of water as the nucleophile attacking the oxirane ring, a methylating reagent were substituted, then perhaps an analogous alkylated lactone



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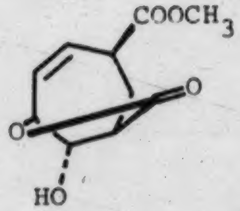

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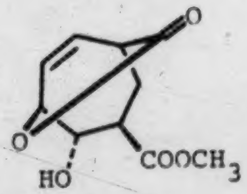
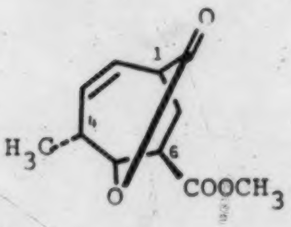


232

could be isolated. We found this to be the case. To minimize the possibility of concurrent epimerization of one of the carbomethoxy groups, lithium dimethylcuprate was chosen for the methyl source. Thus as described above, the diacid 214 was converted to a mixture of 227, 228, and methyl m-chlorobenzoate. Without further purification the mixture was added to a cold solution of lithium dimethylcuprate. Reaction appeared to proceed immediately, with the formation of a heavy yellow precipitate. Hydrolysis in aqueous ammonium chloride solution followed by careful chromatography on silicic acid gave a 35% yield of a colourless oil which solidified slowly. Recrystallization of the solid afforded an analytically pure alkylated lactone (mp 64.0-65.0°) in an overall yield of 27-30% from the cycloheptadiene dicarboxylic acid.

Transformation of the monoepoxide diesters into the methylated lactone was to be a key step in the synthesis of (±)-32. Much of the credit for the development of this reaction belongs to Dr. Kim. Later Drs. Davis and Yamamoto introduced significant improvements in the experimental procedure.

Several isomeric structures for the lactone were examined. These are shown as 233-236. Only one isomer, namely 233, was of use to us in further work. It was therefore important to establish the structure of our lactone with as much certainty as possible.



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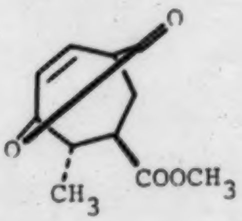

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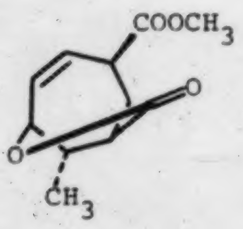

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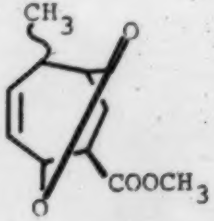
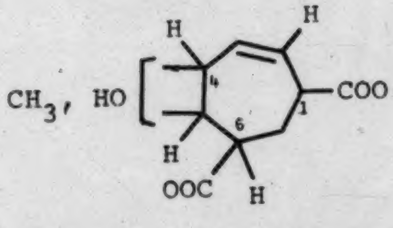


236

On the basis of the known course of the methylation of the model substrate 223, structures 234 and 235 were considered highly unlikely. Analysis of the ir and nmr spectra of the lactone provided strong evidence for structure 233. The ir spectrum ($CHCl_3$) exhibits a broad maximum at 1741 cm^{-1}. This value falls within the expected range for a δ-lactone and thus provides the first piece of evidence ruling out the γ-lactone 235 (normal C=O str., 1780-1760 cm^{-1}). All isomers with a β-lactone moiety (not shown above) can be confidently excluded. The assignment of the nmr spectrum to 233 is shown in Table 4. The interpretation of the decoupling results is complicated by the coincidence of the chemical shifts of H_4 and H_6 and by the presence of long-range couplings involving the olefinic protons. The position of $C\underline{H}-CH_3$ (τ *ca.* 7.03) is located by irradiating the high-field methyl group. Decoupling the low-field olefinic proton (τ 4.19) strongly affects the $C\underline{H}COO-$ (ester or lactone) signal at τ *ca.* 6.86. There is no accompanying change in the nearby two-proton absorption at τ *ca.* 7.03 ($C\underline{H}-CH_3$ and the other $C\underline{H}COO-$). Back-irradiation at τ 6.86 removes an 8.5 Hz coupling in the low-field olefinic proton. Therefore the first $C\underline{H}COO-$ must be adjacent to the double bond (partial structure A),



Partial Structure A

thereby eliminating possibility 236. Irradiation at τ 7.03 reveals a long-range coupling (2.2 Hz) between H_2 and $C\underline{H}$-

Table 4: Nmr Analysis (100.1 MHz, $CDCl_3$) of Lactone **233**

Proton Irrad'd	Chemical Shift (τ) and Multiplicity[a] (Hz) H_2[b,c]	H_3[b]	H_5	$COOC\underline{H}_3$	H_1	$H_{4,6}$	$H_{7,7'}$	C_4-$C\underline{H}_3$
	4.19	4.48	5.22	6.25	6.86	7.03	7.51	8.87
	d,10.5	d,10.5	cd,3.7	s	m	m	m	d,7.3
	d, 8.5	d, 0.9	d,1.0					
	d, 2.2	t, 1.5						
C_4-$C\underline{H}_3$	--	--	--		--	**	--	
$H_{4,6}$	d,10.5	d,10.5	d,1.0					s
	d, 6.0	d, 1.5						
H_5	--	d,10.5			--	**	--	
		d, 2.2						
H_2			--		**	--	--	
H_1	d,10.5	d,10.5	*				**	
	d, 1.2	t, 1.5						

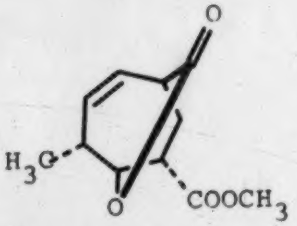
a) For an explanation of the multiplicity abbreviations see page 204, Chapter 10.

b) The splitting pattern is not first order. However for comparison of the effects of double resonance studies, a visual interpretation of the multiplicity and the coupling constants has been included.

c) The partial collapse of coupling constants in the H_2 absorption, observed during irradiation at $H_{4,6}$ or H_1, probably results from the unavoidable perturbation of the overlapping signals of H_1 or $H_{4,6}$ respectively.

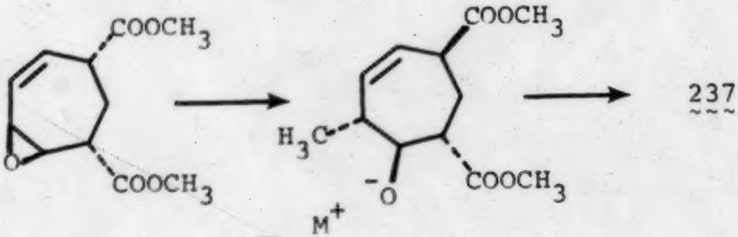
CH_3. The size of the coupling constant can be rationalized only if the methyl group is attached to C_4. The conclusion is reached that 233 is the correct structure.

Although the constitution of the lactone had been established as 233, there was a small, but distinct possibility that the lactone did not have the stereochemistry implied in structure 233. The other configurational possibility 237 was the C_6 epimer of 233. The reason for suggesting that the lactone might be 237 was based on an experiment to examine the stability of dimethyl cis-4,6-cycloheptadiene-1,3-dicarboxylate (213) towards lithium dimethylcuprate. After treating 213 with the cuprate in a manner similar to the lactone reaction, the mixture was decomposed at low temperature with a solution of acetic acid in ether. (Equimolar amounts of methyllithium, used to generate the cuprate salt, and of acetic acid were employed.) Final hydrolysis with water gave a reaction mixture with a pH of 5.5-6.0. After isolation, the dimethyl ester was analysed by nmr spectroscopy. Approxi-



237

mately 18% of 213 had epimerized. (Epimerization during work-up is unlikely since it had been shown in another study that both the *cis* dicarboxylic acid 214 and its diester 213 are stable towards a methylene chloride solution of *m*-chlorobenzoic acid.*) Compound 237 might arise therefore if the allylic carbomethoxy group of the *trans* allylic epoxide epimerizes when treated with the cuprate,



228 238

either before or after the cleavage of the oxirane. Nevertheless, we did not consider 237 likely to be the structure of the lactone. Only 18% epimerization occurred during extended stirring (5 hr) of 213 with the lithium cuprate whereas, starting from a 1:1 mixture of *cis* and *trans* allylic epoxides, the lactone is isolated in 27-30% yield after a reaction time of only 30-45 minutes. In conclusion we felt quite confident the structure 233 represented our lactone.

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*The purpose of this work was to convince us that the chances of epimerization during the epoxidation reaction were slight.

The lactone was an important intermediate. All of the stereochemistry contained in 200 had now been introduced. The next stage in the synthesis was the reduction of the carbomethoxy groups to methyl groups.

A number of methods to reduce an ester to a methyl group are known. The two most common routes are indicated below. Various reagents are available for carrying out the final step in both routes. Unfortunately most of these reagents (e.g. lithium aluminum hydride, sodium borohydride, catalytic hydrogenation, active metals) have rather broad spectra of reactivity towards various functional groups. Therefore undesirable transformations at other locations on the substrate may occur during the reduction.

Route 1:

$$RCOOR' \longrightarrow RCH_2OH \longrightarrow RCH_2X \longrightarrow RCH_3$$

X=sulphonate, halide, SR"

Route 2:

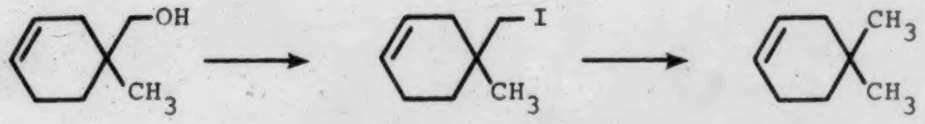
$$RCOOR' \longrightarrow RCHO \longrightarrow RCH{=}Y \longrightarrow RCH_3$$

$Y=R''N,\ (R''S)_2$

In 1971 Hutchins and coworkers[111] reported that sodium cyanoborohydride ($NaBH_3CN$) dissolved in hexamethylphosphoramide (HMPA) is capable of reducing, under very mild conditions, tosylates, bromides, and iodides to the corresponding hydrocarbons. The reported yields are excellent--many yields were greater than 90%--and the reagent is inert to most of the other common functional groups (*e.g.* aldehyde, epoxide, ketone, nitrile, and ester). The ease of the reduction follows the order:

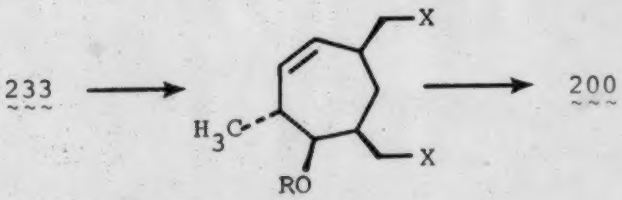
I > Br > OTs.

In an impressive example, the authors reported the conversion of the neopentyl alcohol **239** to **241**, via the iodide **240**. The overall yield is 58%.



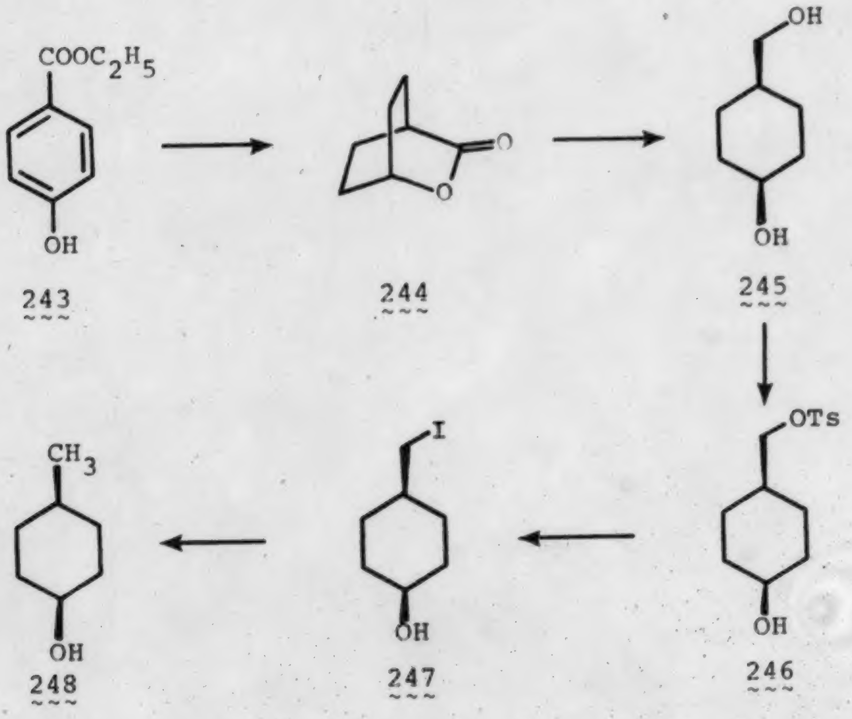
239 **240** **241**

If the lactone were converted to **242**, sodium cyanoborohydride appeared to be an ideal reagent to get to **200**.



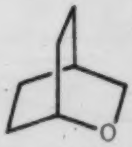
242: X=I, Br, or OTs

Dr. G. Spessard in our laboratory tested the plan on the model compound **247**. The synthesis of **247** was straightforward (Scheme 9). The known substance 1,4-cyclohexanecarbolactone (**244**), prepared from ethyl p-hydroxybenzoate,[112] was reduced by lithium aluminum hydride to the cis diol **245** which was then converted in 73% yield to the primary



tosylate **246**. Subsequent treatment of **246** with anhydrous sodium iodide in refluxing acetone did give **247**, but the reaction was slow and the yield was only 59%. When a solution of the iodide **247** and commercial sodium cyanoborohydride in dry hexamethylphosphoramide was stirred at room temperature, no reaction occurred. However by simply warming the solution to 70°, reduction proceeded smoothly. After heating overnight, a product was isolated. Living up to Hutchins' claims, the crude product, isolated in 89% yield, proved to be cis-methylcyclohexanol (248), contaminated with only traces of impurities.

During the reduction the hydroxyl group of 247 had been left unprotected. That only a trace at most of the bicyclic ether 249 was formed, attests to the very mild



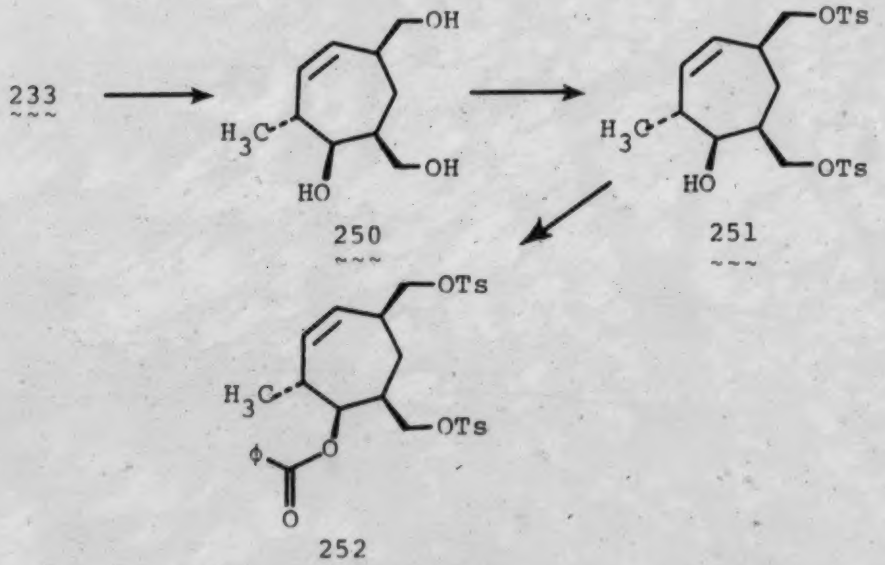
249

nature of the cyanoborohydride reagent.

The analogous reduction of the tosylate 246 did not proceed well. Forcing conditions (extended heating at 120°) were necessary, 248 was formed in only 30% yield, and no starting material was recovered.

The preparations of 245-248 are included in the experimental section (Chapter 10).

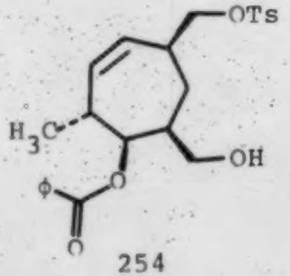
The general sequence of Scheme 9 was then applied to lactone 233. Reduction of 233 with lithium aluminum hydride gave a viscous, oily triol (250). After scrupulous drying, a pyridine solution of the triol was treated with two mole equivalents of *p*-toluenesulphonyl chloride. Standard work-up and rapid chromatography on silicic acid afforded a pure ditosylate (251) in 75% yield from 233. The nmr spectrum of the ditosylate showed that, as expected,



both tosyloxy groups are primary. The OH stretching band in the ir spectrum (0.1 cm NaCl, $CHCl_3$) of 251 appears as a triangular peak at 3570 cm^{-1}. Apparently the hydroxyl is strongly hydrogen-bonded with a tosyloxy group or with the double bond.

Compound 247 had been successfully reduced to 248 without prior protection of the alcohol function. In the final cleavage of the double bond of the cycloheptene system [200→(+)-32], we thought that protection of the hydroxyl group would likely be necessary. By introducing the mask at the present stage in the synthesis, it would then serve also as insurance against complications in the cyanoborohydride reaction. In dry pyridine at 0°, the reaction of 251 and benzoyl chloride was remarkably slow. Twenty-four hours were required for the complete disappearance of starting material. The crude product, after the customary work-up procedure, was freed of benzoic anhydride and small amounts of impurities by chromatography on silicic acid. Pure 252 was obtained as a colourless oil in 90% yield. Noteworthy about the nmr spectrum ($CDCl_3$) of 252 is the upfield shift of one of the aryl methyl singlets. While the two aryl methyl peaks are coincident (τ 7.55) in the nmr spectrum ($CDCl_3$) of 251, the two signals are well separated in the spectrum of the benzoate (τ 7.55 and τ 7.66). Presumably the *p*-methyl substituent of the tosyloxymethyl group vicinal to the benzoate experiences anisotropic shielding from the neighbouring aromatic nucleus.

Both 251 and 252 decompose to a greater or less extent if their chromatographic purification is prolonged unnecessarily. The hydroxy ditosylate is transformed into a substance (253) having a larger R_f value on silica gel and silicic acid. The structure remains obscure but nmr results ($CDCl_3$) suggest that two tosyloxy groups are present. A high-field methyl doublet (τ 9.06, J=7.3 Hz) is also evident. The fate of the benzoyloxy ditosylate upon decomposition is the hydrolytic product 254. Comparison



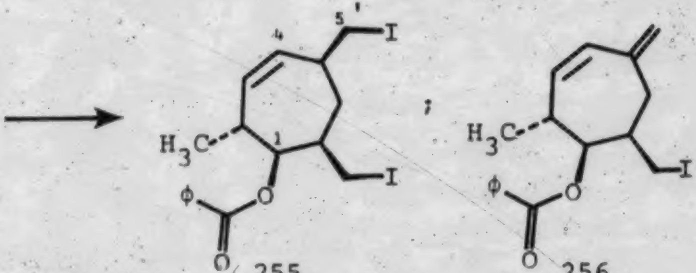
254

of the nmr spectra ($CDCl_3$) of 252 and 254 reveals that the four-proton multiplet at τ 6.06 in 252 has been replaced by a two-proton doublet (τ 5.98, J=6.5 Hz). A new, complex, two-proton doublet (J=8.5 Hz) has appeared at τ 6.60, a value characteristic of $-C\underline{H}_2OH$. In addition, the high-field aryl methyl singlet (τ 7.66) in 252 has vanished, being replaced by a hydroxyl proton. In all other aspects the spectra of 252 and 254 are very similar.

Sodium iodide-acetone had afforded only a 59% yield of iodide 247. In an effort to improve the displacement reaction, both from a standpoint of reaction rate and of yield, other experimental conditions were investigated. We have found that by refluxing an acetonitrile solution containing an organic tosylate and anhydrous lithium bromide, the corresponding bromide is produced in excellent yield. In an analogous manner, a solution of

252 and anhydrous lithium iodide in dry acetonitrile was heated under nitrogen. Upon reaching reflux temperature, the solution had become orange (the presence of I_2) and a white precipitate, presumably lithium tosylate, had formed. After 3.5 hr, tlc (silica gel) showed that no starting material remained. A single new spot exhibiting a large R_f value had appeared. The crude product was isolated as a pale yellow oil. Nmr analysis showed the product to consist mostly of the desired diiodide **255**. However a significant amount of impurity was also present.

252



255 **256**

The impurity appears in the nmr spectrum (100.1 MHz, $CDCl_3$) as at least eight sharp singlets, distributed from high to low field, the strongest singlets occurring at τ 4.64 and τ 7.68. These extraneous peaks undoubtedly reflect reaction complications arising from the solvent, acetonitrile. Chromatography of the crude diiodide on silicic acid does not partition the impurity and the desired product. In addition to the integral behaviour of the impurity and the product on chromatography, the nmr spectrum reveals that only 75% of the product that contains a benzoyloxy group also contains a disubstituted double bond. These results would infer that the side reactions which involve acetonitrile also, to at least some extent, implicate the double bond of the cycloheptene system. As the simplest explanation, the presence of the iodine, which is responsible for the orange reaction colour, and/or an unnecessarily long reaction time might be to blame for the complications. The experiment was therefore repeated.

The reaction was carried out in the presence of mercury[113] to remove the iodine formed and the disappearance of the starting ditosylate was carefully monitored. Under these conditions, the refluxing reaction mixture remained completely colourless and no starting material was detected after only 18 minutes. During work-up, mercury salts were removed by washing a benzene--pentane solution of the crude diiodide with aqueous sodium thiosulphate solution. The product then needed only filtration through a small column of silicic acid. The diiodide 255 was obtained as a colourless oil in excellent purity in 92% yield. Analysis of the nmr spectrum of 255, summarized below in Table 5, fully supports the assigned structure.

The chemical shift of H_2 is revealed by irradiating the methyl doublet. The methine protons H_5 and H_7

are identified by the decrease in the half-height width of the two-proton multiplet at τ 7.50 when the symmetrical absorption, attributed to the C_6-methylene group, is irradiated. When the spectrum is decoupled from $C\underline{H}\text{-}CH_3$, there is a marked collapse of both the $C\underline{H}\text{-}O$ and the olefinic signals. Thus $C\underline{H}\text{-}CH_3$ must be straddled by an olefinic proton* and by the methine proton geminal to the benzoyloxy group. (The chemical shifts of H_2 and H_5 are sufficiently different not to cause any ambiguity in the interpretation of the results.) The appearance of $H_{7'A}$ and $H_{7'B}$ (note c, Table 5) suggests that the chemical shifts of the two protons are quite different. The spectrum obtained when H_5 and H_7 are simultaneously irradiated hints that the chemical shifts of $H_{7'A}$ and $H_{7'B}$ are roughly τ 6.77 and τ 6.90 respectively. The assignment of $H_{5'A,5'B}$ and $H_{7'A,7'B}$ is based on the assumption that it is more reasonable to expect the iodomethyl protons adjacent to the benzoyloxy group to show greater chemical non-equivalence. This assumption is strengthened by the nmr spectrum ($CDCl_3$) of 256 which also shows the iodomethyl pro-

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*The collapse of the olefinic absorption seems too extensive to be due to the removal of a small coupling constant ($J \leq 2$ Hz), which could be attributed to a long-range coupling between $=C\underline{H}-$ and $-C\underline{H}CH_3$.

Table 5: Nmr Analysis (100.1 MHz, $CDCl_3$) of Diiodide 255

Proton Irrad'd	Chemical Shift (τ) and Multiplicity[a] (Hz)								
	H_{aryl}	$H_{3,4}$	H_1	$H_{5'A,5'B}$	$H_{7'A,7'B}$	H_2	$H_{5,7}$	$H_{6A,6B}$	C_2-CH_3
	1.80-2.83	4.52	4.59	ca. 6.70	ca. 6.83	ca. 7.04	7.50	8.11	8.89
	m	m	d,2.5	m[b]	m[c]	m	m	m	d,7.3
			d,6.0						
C_2-CH_3	--	--	--	--	--	cd,6.0	--	--	
H_2	--	bs	bd,2.5					--	--
$H_{6,6}$	--	--	--	--	--	--	*		--
$H_{5,7}$	--	--	--	bs	**			**	--

a) For an explanation of the multiplicity abbreviations, see page 204, Chapter 10.

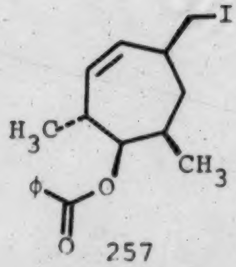
b) Visually the $C_{5'}$ protons appear as a doublet (J=5.5 Hz) however overlap with signals of either $H_{7'A}$ or $H_{7'B}$ prevents expressing the multiplicity more precisely.

c) The $C_{7'}$ protons appear as a series of sharp signals over the range τ 6.64-6.96.

tons as a broad series of sharp signals (τ 6.40-6.75).

An attempt to prepare the diiodide 255 by heating for 1.0 hr at 55° and 1.0 hr at 90° a solution of 252 and sodium iodide in wet hexamethylphosphoramide[114] gave exclusively a single, new compound which almost certainly must be 256. Strong evidence for this structure is derived from its nmr spectrum ($CDCl_3$) which indicates the presence of a benzoyloxy group, an aliphatic methyl doublet (τ 8.85, J=7.0 Hz), and a four-proton olefinic pattern characteristic of the diene moiety in 256. (The olefinic absorption is very similar to that observed for 260.) The two-proton "doublet" (see note b, Table 5) observed for the allylic iodomethyl group ($H_{5'A,5'B}$ of 255) is not present although, as noted above, the complex splitting pattern of the $C_{7'}$ protons is very evident. Mechanistic arguments also support 256 since the homoallylic tosylate and iodide portions of 252 and 255 should be prone to elimination under basic conditions. The reaction solvent, HMPA, is well known to possess basic properties.[115] Cyclohexene is formed in 62% yield by heating cyclohexyl tosylate in HMPA at 100° for 6 hr.[116] Dehydroiodination of 255 and/or 257 has also been observed (*vide infra*).

The diiodide, now obtainable in a fast, high-yield reaction, was next subjected to Hutchins' reaction. In the first attempt to reduce 255 to 258, the reaction



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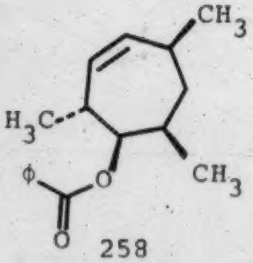
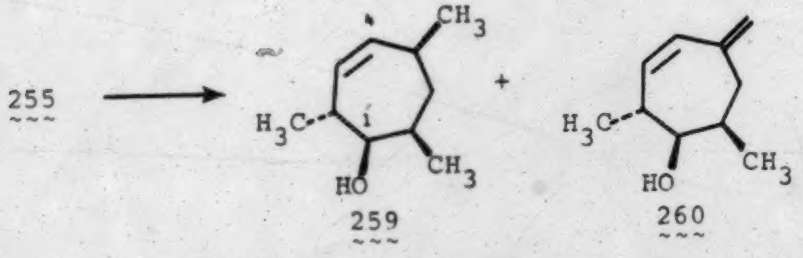


258

conditions that had successfully reduced 247 were employed. The reaction was worked-up after 17 hr heating at 70-75°. No iodomethyl protons were seen in the nmr spectrum of the crude product. However the spectrum showed the product to be a mixture of compounds. By glpc (UCW-98) two major substances were present in approximately a 1:1 ratio. To separate the mixture, the benzoyloxy group was first removed in refluxing methanolic sodium methoxide and the resulting alcohols were effectively separated by chromatography on silicic acid. Gratifyingly, the first alcohol to be eluted exhibited an nmr spectrum (100.1 MHz, $CDCl_3$) entirely consistent with the desired trimethylcycloheptenol 259. Most important of the features are a two-proton olefinic multiplet at τ 4.48, a one-proton doublet of doublets at τ 6.43, and three methyl doublets at τ 8.90-9.05. Furthermore the mass spectrum of the alcohol has an apparent parent ion at *m/e* 154 (P for 259). The second alcohol shows an apparent molecular ion at *m/e* 152 (P for 260).



Evidence for structure 260 is provided by its nmr spectrum (CCl_4). The olefinic pattern is consistent with the structure of the diene moiety in 260. There are multiplets at τ 4.11 (1H), 4.85 (1H), and 5.24 (2H). A doublet of doublets (1H, J=8 Hz and 3 Hz) is evident at τ 6.63 as well as two well-separated methyl doublets (τ 8.92, J=7.5 Hz and τ 9.10, J=7.3 Hz) at higher field. A broad five-proton multiplet at τ 7.4-8.4 completes the spectrum.

From the results of the reduction experiment it was obvious that dehydroiodination presented a problem. However it was not at all clear whether it was the basic nature of the cyanoborohydride ion (or of similar tetravalent boron species) or of HMPA that had been responsible for the elimination. A third possibility was that the commercial sodium cyanoborohydride contained boric acid[117] as an impurity which might have catalysed the elimination.

To remove any boric acid and/or sodium borohydride,[111] the reducing agent was recrystallized twice from tetrahydrofuran--methylene chloride.[117] If HMPA were involved in the elimination mechanism, then presumably the proportion of elimination product should be decreased by making the oxygen atom of HMPA less basic. To accomplish this, one approach was to reduce the amount of HMPA used in the reaction to the point that the mole ratio HMPA: $NaBH_3CN \leq 1.0$. The reasoning behind this was that most, if not all, of the phosphoramide oxygen atoms would then be involved in the strong solvation of the sodium cations.* In this way, HMPA should become less efficient at promoting elimination but still serve its prime role of supplying cyanoborohydride anions of high nucleophilicity.

The reduction was repeated. Dimethoxyethane was used as solvent; the mole ratio of reagents was

$$\underset{\sim\sim\sim}{255}:NaBH_3CN:HMPA = 1:10:9.$$

The reduction at 75° proceeded slowly, requiring 30-40 hr. The glpc trace (UCW-98) of the crude product showed four compounds. One of the two main benzoates that had been

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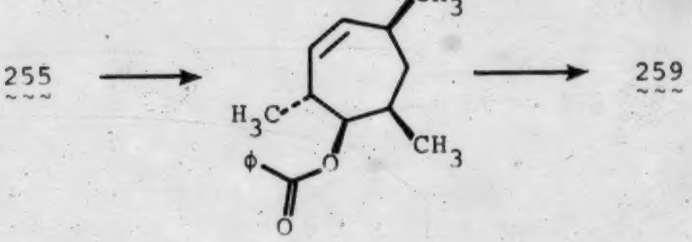
*HMPA in benzene solubilizes lithium bromide. The equilibrium constant for the complexation process

$$HMPA + LiBr \rightleftharpoons [HMPA...LiBr]$$

is known to be significantly greater than unity.[118]

obtained in the previous experiment now composed *ca*. 81% of the mixture. The other benzoate represented only 4% of the crude product. No signals attributable to the diene moiety in the benzoate of **260** could be seen in the nmr spectrum. The spectrum was in full accord with structure **258**. The absolute yield of **258** was *ca*. 72%. (When com-



258

mercial sodium cyanoborohydride, which had not been previously purified, was used, the proportion of diene in the crude product rose to only 8%.) Crude **258** was purified in the same manner as before, namely by transesterification to **259** and chromatography. Surprisingly strenuous conditions were necessary to effect the transesterification. Table 6 summarizes the nmr data of **259**.

The OH stretching region in the ir spectrum of **259** reveals strong intramolecular hydrogen-bonding (3581 cm^{-1}) at normal sample concentrations.

The final stage of the synthesis (**200**→**32**) had now been reached. Cleavage of the double bond in **200** was accomplished by Lemieux-von Rudloff oxidation (sodium

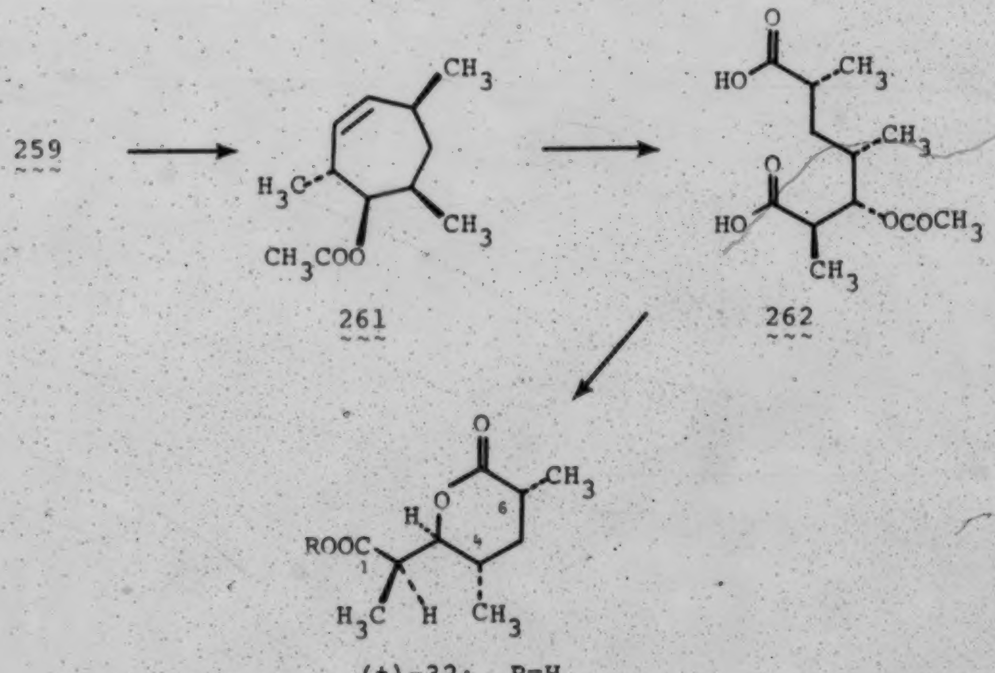
Table 6: Nmr Analysis (100.1 MHz, $CDCl_3$) of **259**

Proton Irrad'd	Chemical Shift (τ) and Multiplicity[a] (Hz)									
	$H_{3,4}$	H_1	H_2	H_5	H_7	OH	$H_{6A,6B}$	C_2-CH_3	C_5-CH_3	C_7-CH_3
	4.48	6.43	7.41	7.65	7.96	8.16	8.71	8.94	8.97	8.98
	m	d,2.0 d,6.0	m	bs	bs	bs	m	d,7.2	d,7.2	d,7.0
$H_{3,4}$		--	**[b]	*[b]	--	--	--			
H_1			**	--	**[b]	--	--			
H_2								**	--	--
H_5								--	**	--
H_7								--	--	**

a) For an explanation of the multiplicity abbreviations, see page 204, Chapter 10.

b) The multiplet has a basic quartet structure.

periodate and potassium permanganate).[119] Although it may be possible to carry out the oxidation directly on 259, prudence convinced us to first replace the hydroxyl-protecting group. Pyridine and acetic anhydride converted 259 into the acetate 261. The acetate, obtained in 94% yield after distillation, was at least 95% pure by glpc analysis


CH$_3$
H$_3$C
CH$_3$
CH$_3$COO
O
HO
CH$_3$
CH$_3$
O
HO
OCOCH$_3$
CH$_3$
O
CH$_3$
H
O
6
ROOC
1
4
H$_3$C
H
CH$_3$

259

261

262

(±)-32: R=H

(±)-37: R=CH$_3$

(Reoplex). Oxidation of 261 in an aqueous *tert*-butanol solution of sodium periodate and potassium permanganate, adjusted to pH 8.5 with potassium carbonate, afforded the acetoxy dicarboxylic acid 262 as a white crystalline solid in 98% yield. This was the first solid compound which had been isolated since the lactone 233. A single recrystallization gave analytically pure 262 (mp 110.1-111.0°). The high resolution mass spectrum of the dicarboxylic acid exhibits a parent ion at *m/e* 260.1255, corresponding to the required molecular formula $C_{12}H_{20}O_6$. The nmr and ir spectra of the product are also in complete accord with 262.

As had been previously observed for 258, the removal of the hydroxyl-protecting group in 262 was difficult. Only by refluxing the acetate for 4 hr in 0.5 *M* methanolic sodium methoxide was the acetyl moiety successfully split off. After acidifying to pH 1 and stirring for 30 min, a white, crystalline lactonic acid was isolated in 86% yield after chromatography on silicic acid. An analytically pure specimen (mp 112.0-113.0°) was obtained after one recrystallization. The nmr and solution ir spectra of the lactonic acid are identical in all respects to those of the natural Djerassi-Prelog lactonic acid (+)-32. [Samples of (+)-32 were kindly provided by Professors V. Prelog and C. Djerassi.] Furthermore, the corresponding methyl esters, (±)-37 and (+)-37, prepared using ethereal diazomethane, exhibit identical nmr and ir spectra. Because the lactone ring imposes conformational constraints on 32 and 37, we feel that the various possible diastereoisomers should display very different patterns for the three methyl doublets. Indeed this is the case for the four diastereoisomers 113a-d, prepared by Bergel'son and Batrakov.[18b] The six methyl lines in the spectra of (+)-32, (±)-32, (+)-37, and (±)-37 were calibrated. Agreement in chemical shifts between the pair of acids and the pair of esters was excellent. For example, Table 7 lists the data for the methyl esters. The results of an nmr study of (±)-32 are summarized in Table 8.

Table 7: Chemical Shifts (100.1 MHz, CCl_4) of the Methyl Signals in (±)-37 and (+)-37

Methyl Signal	Chemical Shift (Hz) from TMS	
	(±)-37	(+)-37
1	125.6	125.9
2	119.9	119.8
3	119.6	118.9
4	113.4	112.9
5	102.4	102.3
6	96.3	96.0

On the evidence presented in this chapter, we feel confident that our synthetic lactonic acid is the

Table 8: Nmr Analysis (100.1 MHz, CCl_4) of (±)-32

Proton Irrad'd	Chemical Shift (τ) and Multiplicity[a] (Hz)									
	COOH	H_3	H_2	H_6	H_{5A}	H_4	H_{5B}	C_6-CH_3	C_2-CH_3	C_4-CH_3
	1.3 bs	5.42 d, 2.4 d,10	7.26 q,7.1 d,2.4	7.51	*ca*.8.0 m	*ca*.8.1 m	*ca*.8.55 m	8.72 d,6.9	8.81 d,7.2	8.99 d,6.9
H_3			q,7.1	--	--	**	--			
H_4		**					**	--	--	bs
H_2		d,10			--		*[b]	--	s	--
H_6		--			**		**	bs	--	--
H_{5A}							**			

a) For an explanation of the multiplicity abbreviations, see page 204, Chapter 10.

b) Likely the H_2-decoupling frequency was overlapping a portion of the H_6 signal. A small effect of H_{5B} is observed.

racemic form of the Djerassi-Prelog degradation product. Moreover, it is now apparent that not one of the four nmr spectra (60 MHz, $CDCl_3$) of the diastereoisomeric lactonic acids 113a-d matches the spectrum (60 MHz, $CDCl_3$) of 32.

The synthesis of (±)-32 from the intermediate lactone 233 has been achieved in an overall yield of 23%.

CHAPTER 8

AN IMPROVED SYNTHESIS OF CIS-4,6-CYCLOHEPTADIENE-1,3-DICARBOXYLIC ACID

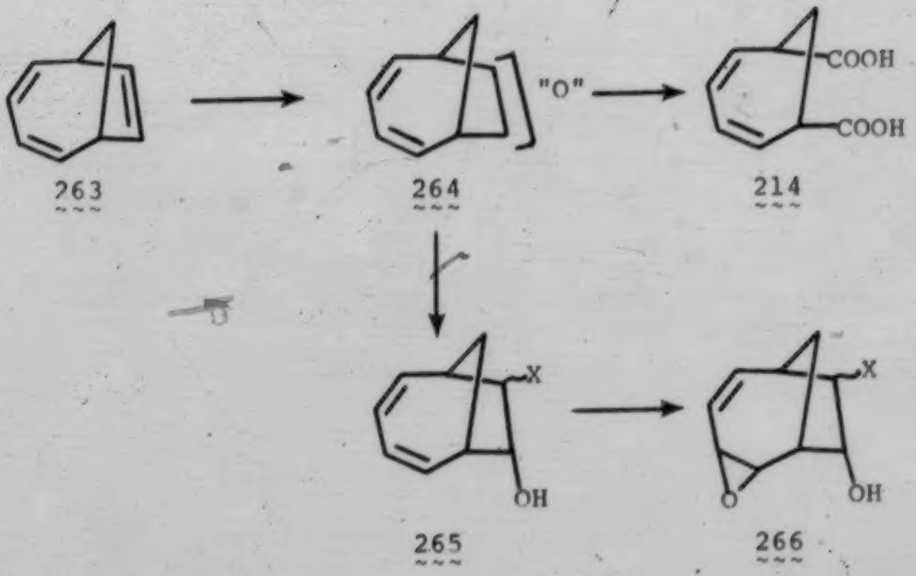
AND

THE FEASIBILITY OF INTRAMOLECULAR EPOXIDATION

The synthesis of racemic lactonic acid (±)-32 described in the preceeding chapter has two practical drawbacks. The inconvenience of the large-scale preparation of 3,5,7-cycloheptatriene-1,3-dicarboxylic acid (201) has been discussed previously. The second critical weakness is the non-stereospecific epoxidation of 214. Although the subsequent methylated lactone 233 can be isolated without much difficulty, the low yield (*ca.* 30%) makes its preparation not very economical both in time and in reagents.

A potential method to solve both problems was suggested by some work published by Cannell in 1966.[120] He reported that bicyclo[4.2.1]nona-2,4,7-triene (263) is formed during the pyrolysis of the $[{}_{\pi}2_s + {}_{\pi}2_s]$ dimers of norboradiene. If the isolated double bond of 263 could be selectively oxidized, then a means to oxidatively cleave the C_7-C_8 bond should be possible, thereby leading directly to the lactonic acid intermediate 214 (Scheme 10).

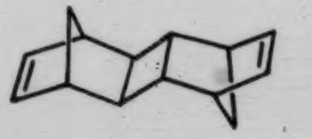
Scheme 10



Alternatively, the introduction of an endo C_7-hydroxyl in the bicyclic system would produce a substrate that may undergo predominantly endo epoxidation. The endo epoxide 266 (and/or the other possible endo epoxide) could then be directed to the lactone 233 or its equivalent.

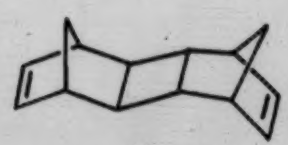
An Improved Synthesis of Dicarboxylic Acid 214

Cannell prepared the dimeric starting materials by heating norboradiene with metal carbonyls (Fe, Co, and Ni) as catalysts. It had been known[121] that this procedure produces exclusively the *anti*-fused $[_{\pi}2_{s} + _{\pi}2_{s}]$ dimers (see 267, 268, and 269). The relative proportions



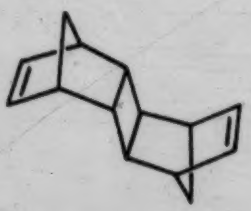
exo-*anti*-*exo*

267



exo-*anti*-*endo*

268

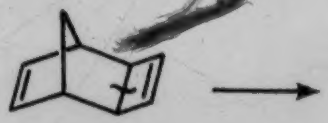


endo-*anti*-*endo*

269

of 267, 268, and 269 depend upon the metal catalyst used. An added advantage in the synthesis of 263 is that a mixture of norboradiene dimers has recently become commercially available at modest cost from Aldrich Chemical Company, Inc. Although the origin of the commercial dimers is not known, the nmr spectrum is easily interpreted as a mixture of 267 (19%), 268 (74%), and 269 (7%). Comparison was made with the spectra of the pure dimers, reproduced in reference 121. Glpc analysis (UCW-98) indicated three compounds in approximately the above proportions.

Cannell mentioned that 268 and 269 are converted readily to 263 at 450° in a flow system. The *exo*-*anti*-*exo* isomer (267) however is much less reactive. These observations are consistent with our own. Pyrolysis at 450° and fractional distillation of the crude pyrolysate gives 263 in 42% yield. The pot residue after the distillation contains unreacted dimer which can be purified by recrystallization. The nmr spectrum of the recovered dimer is identical to that reported for *exo*-*trans*-*exo* dimer **267**.[121] When the dimer mixture is pyrolysed at lower temperatures (*e.g.* 400°), a small amount of *exo*-tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene (**270**) is isolated during the distillation. Compound **270** was identified by its reported nmr spectrum.[120] Again



263

270

this observation is in line with Cannell's results. The pyrolysis experiments were performed by Dr. H. Davis. Presumably the formation of **263** involves a retro-Diels Alder reaction of the dimers to give **270**. Thermolysis of the cyclobutene ring leads to **263**.

The oxidation of **263** with *m*-chloroperbenzoic acid was first investigated. Hydrolysis of the desired 7,8-epoxybicyclo[4.2.1]nona-2,4-diene would give hopefully a compound useful as an intermediate to both **214** and **233**. The nmr spectrum of **263** exhibits a narrow multiplet for the two protons of the isolated double bond at higher field (τ 4.87) than the broad complex multiplet of the conjugated diene protons (τ 3.68-4.51). After **263** had been treated for one hour at 0° with one mole equivalent of m-chloroperbenzoic acid in methylene chloride, the multiplet at τ 4.87 had disappeared. However glpc (Reoplex) showed the product to be approximately a 1:1 mixture of two substances, 271 and 272.

Compound 271, which has the shorter retention time, was successfully isolated by chromatography on silicic acid. On the basis of the uv and nmr spectra (see Table 9), we concluded that 271 is the desired 7,8-epoxybicyclo[4.2.1]nona-2,4-diene. The exo isomer is favoured, because of the inertness of the epoxide to refluxing methanolic sodium methoxide. In contrast to 271, compound 272 is decomposed by both silicic acid and methanolic sodium methoxide. Although 272 has not been isolated in a pure form, it was concluded that 272 does not contain a conjugated diene chromophore. This follows from the fact that the quantitative features of the uv spectrum of the mixture can be explained completely in terms of the spectrum of 271, assuming that 271 constitutes 40% of the mixture. The exact structure of 272 remains uncertain. Since peracid oxidation of 263 does not produce cleanly the desired product, this approach was abandoned.

The monohydroboration of 263 was next examined. An advantage of this method of functionalizing a double bond is the high improbability of skeletal rearrangements.

Table 9: Nmr and Uv Data of Compound 271

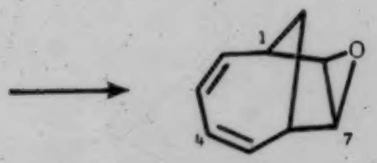
Uv Spectrum (methanol):

λ_{max} 278 nm (ε=4600), 267 nm (ε=*ca*.7100), 256 nm (ε=6600), 248 nm (ε=4500).

Nmr Spectrum (100.1 MHz, $CDCl_3$):

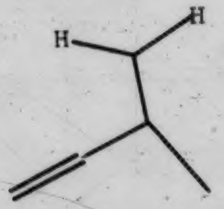
Chemical Shift (τ) and Multiplicity[a] (Hz)				
H_{2-5}	$H_{7,8}$	$H_{1,6}$	H_{9A}	H_{9B}
4.15	6.56	7.04	7.97	8.50
m	s	bt,*ca*.6	d,12.1	d,12.1
			t, 6.0	

a) For an explanation of the multiplicity abbreviations, see page 204, Chapter 10.

263  + 272 ?

271

The alcoholic products, obtained after oxidative work-up, were expected to be less prone to rearrangements than the epoxy products.* However we could not predict how selective the hydroboration would be and, in fact, even what the major product would likely be. The reason for the uncertainty arises because of opposing factors. Cycloheptene is hydroborated by di(isoamyl)borane five times faster than cyclopentene.[122] However in 263, the rate of hydroboration of the seven-membered ring should be reduced somewhat because of the conjugation of the double bonds.



273

In addition, a molecular model of 263 indicates that the methylene bridge is more inclined to the diene plane than to the plane of the isolated double bond. Consequently, the diene moiety is more effectively shielded from *exo* attack by the borane. Both these factors favour attack on the cyclopentene system.

We found that hydroboration primarily occurs at the cyclopentene double bond. Thus the reaction of 263 with one mole equivalent of 9-borabicyclo[3.3.1]nonane[123] afforded the *exo* alcohol 274 in an absolute yield of 75%. Compound 274 however was contaminated by two other products (*ca*. 20%), which exhibited retention times on glpc (Reoplex) very similar to that of 274. These impurities could not be satisfactorily removed. Evidence that the main product has in fact the structure 274 was

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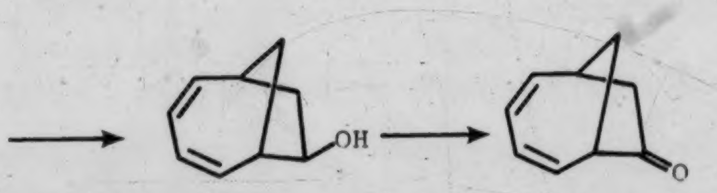
*Both 271 and 272 underwent isomerization during an attempted separation of the mixture by preparative glpc (Diisodecyl Phthalate).

263



274 275

derived from its nmr spectrum (see Chapter 10) and its uv spectrum [$\lambda_{max}(CH_3OH)$ 254 nm, ε=*ca*. 4700]. Molecular models indicate that the *exo* side of the cyclopentene ring is the more exposed to the incoming borane. Accordingly, the hydroxyl group was tentatively assigned the *exo* configuration. The correctness of this assignment is demonstrated at a later point in this chapter. In subsequent experiments, we found that by substituting di(isoamyl)-borane[124] for 9-borabicyclo[3.3.1]nonane, 274 is obtained with improved purity (*ca*. 90%).

Oxidative cleavage of the C_7-C_8 bond first required the introduction of functionality at C_8. To activate the C_8-methylene group, 274 was oxidized to 275 by the Oppenauer method, using aluminum *tert*-butoxide and *p*-quinone. After filtration through silicic acid, the ketone **275** was obtained 98% pure (glpc; UCW-98, Reoplex, Carbowax 20m) and in 80% yield. Spectral data fully support the structure. The uv spectrum* is in accord with a diene chromophore and the ir spectrum contains the expected cyclopentanone band at 1743 cm^{-1}. The nmr data for **275**, **276**, and **277** are presented in Table 10. (Compounds **276** and **277** were prepared from **275** by the controlled stepwise incorporation of deuterium from a solution of sodium in perdeuteriomethanol. Based on mechanistic considerations, the deuterium in **276** was assigned the *exo* orientation.) The absorption at τ 8.24 is assigned to H_{9A} on the evidence of a long-range coupling (J=2.6 Hz) with H_8 (*endo*). This observation also supports the suspected *exo* configuration of the deuterium atom in **276**.

From ketone **275**, the hydroxymethylene derivative **278** was prepared in almost quantitative yield using conventional methods. Oxidative cleavage of α-hydroxymethylene ketones with sodium periodate was first reported by Cornforth, Cornforth, and Popjak.[125] With certain changes in the original procedure, treatment of **278** with sodium

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*The sample of **275** used to obtain the uv spectrum was somewhat impure. A maximum was present at 256 nm (ε= 4200).

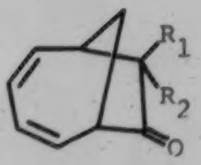
Table 10: Nmr Analysis (100.1 MHz, CD_3OD) of Compounds 275, 276, and 277

Cmpd	Nucleus Irrad'd	Chemical Shift[a] (τ) and Multiplicity[b] (Hz)					
		H_6	H_1	H_8,exo	H_{9B}	H_8,endo	H_{9A}
275		6.68	7.06	← 7.26-7.88 →			8.24
		bt	m[c]		m		cd,12.3
							d, 2.6
276	D	--	bt		7.60	7.72	--
					cd,12.3	cs	
					t, 6.0		
277	D	--	ct,6-7		--		cd,12.3
	H_{9B}	**	**				
	H_6				cd,12.3		--
					d, 6.0		

a) The olefinic protons appear as a multiplet at τ 3.67-4.34.

b) For an explanation of the multiplicity abbreviations, see page 204, Chapter 10.

c) The gross shape of the multiplet is a quartet.



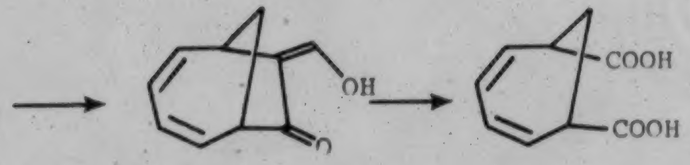
275: $R_1=R_2=H$

276: $R_1=D$, $R_2=H$

277: $R_1=R_2=D$

periodate at pH 4.5-5.0 in aqueous dioxane afforded, after work-up, 214 in 96% yield. The nmr spectrum of the di-

275



278 214

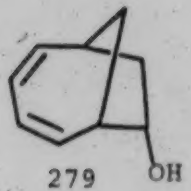
methyl ester of the product showed no evidence of the trans isomer. The very successful hydroxymethylenation and cleavage reactions were due to the efforts of Dr. Spessard.

The synthesis from norboradiene dimers has increased greatly the availability of the cis dicarboxylic acid. Compared with the first synthesis (see Chapter 7), the overall yield is higher and the overall time required is much shorter.

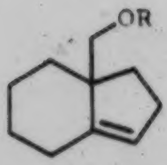
The Feasibility of Intramolecular Epoxidations

Our attempts to effect a stereoselective endo epoxidation in the bicyclo[4.2.1]nonane system will now be described.

With 275 available, an obvious substrate for the epoxidation study is the endo alcohol 279. A study of molecular models pointed out that the relative positioning of the hydroxyl group and the double bond in the homoallylic alcohol 280 is quite similar to the geometry



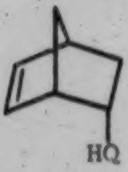
279



280: R=H

281: R=$COCH_3$

in **279**. Marshall and Greene[126] have recently shown that, under certain conditions, the ratio of the *cis* and *trans* epoxides of **280**, prepared using *m*-chloroperbenzoic acid, can be as high as 85:15. Under similar conditions, the corresponding acetate **281** leads to a reversal of the epoxide ratio (30:70). Not to distort the generality of *cis*-directing effects by hydroxyl groups, *endo*-5-hydroxynorbornene (**282**) presents a more sobering example. Reac-

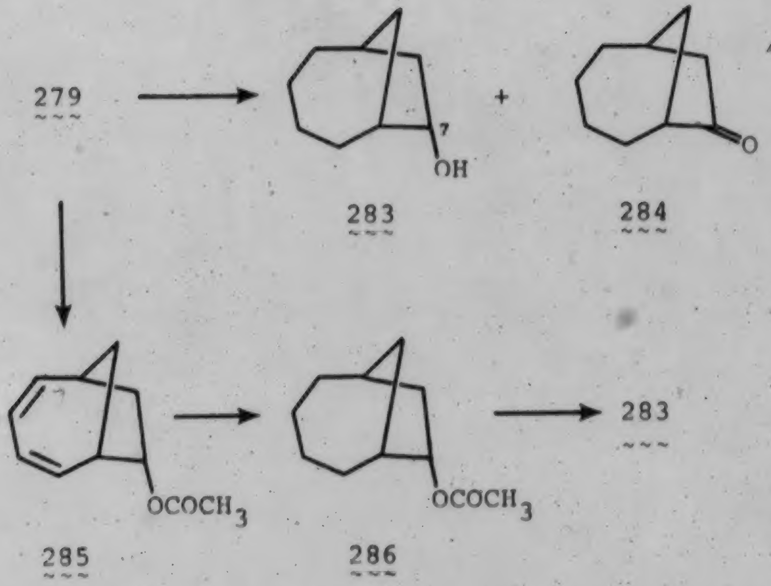


282

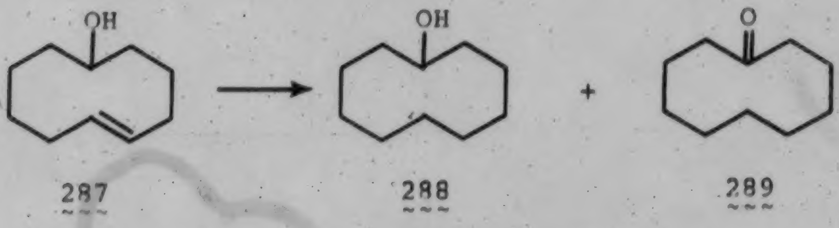
tion of **282** with an ethereal solution of perbenzoic acid gave the *exo* epoxide in 93% yield.[127] Not enough is known about how an organic peracid approaches a double bond to permit reliable predictions concerning product stereochemistry. Nevertheless, the epoxidation of **279** was studied.

Reduction of **275** with lithium aluminum hydride gave exclusively the desired endo alcohol 279 as a white crystalline solid. The uv and nmr spectra of the product are consistent with structure 279. The ir spectrum (CCl_4, ca. 0.59 M) is worthy of comment. In addition to a strong, broad polymeric OH stretching band at 3440 cm^{-1} and a weak free OH absorption at 3630 cm^{-1}, there is a very distinct, third peak at 3582 cm^{-1}. Evidently a hydrogen bond exists between the hydroxyl group and the π-electron system of the conjugated diene. Such occurrences are quite common.[128] At high dilution (CCl_4, ca. 0.0015 M), the spectrum of 279 contains only bands at 3630 cm^{-1} and 3582 cm^{-1}, the latter being somewhat stronger. That the 3582 cm^{-1} absorption is due to hydrogen bonding which involves the diene moiety was confirmed by hydrogenation experiments.

Catalytic hydrogenation of 279 did not proceed smoothly. At atmospheric pressure, using 5% palladium on charcoal in ethyl acetate, greater than a 50% yield of 284 resulted. With platinum oxide in methanol, the proportion of 284 was much less; however it still comprised ca. 5% of the product. The structure of 284 has not been proven rigorously. Nevertheless, on the basis of the ir spectrum (C=O: 1736 cm^{-1}, strong) and a consistent nmr spectrum, the assigned structure seems reasonable. Cope and coworkers[129] observed a similar abnormal product from


279
7
OH
283
284
OCOCH$_3$
285
OCOCH$_3$
286
283

the catalytic hydrogenation of *trans*-5-cyclodecenol (287). Reduction of 287 in methanol, using a palladium catalyst, gave both the alcohol 288 and the ketone 289. The clean


OH
OH
O
287
288
289

reduction of 279 to 283 was successfully accomplished, if not somewhat laboriously, by first acetylating the hydroxyl group to give 285. Hydrogenation and transesterification in methanolic sodium methoxide led to pure 283. As expected, the ir spectrum (CCl_4) of 283 at high dilution exhibits only a single OH stretching band (3630 cm^{-1}).

Additional evidence for the *endo* versus *exo* relationship of 279 and 274 was obtained from an nmr study of the effect of the lanthanide shift reagent,[130a] tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)-europium (III) or more simply $Eu(fod)_3$, on both compounds. Displacement of proton chemical shifts induced by paramagnetic rare earth metal complexes has recently been reviewed.[130b] Carbon tetrachloride solutions of 274 (*ca.* 0.28 *M*), containing various amounts of $Eu(fod)_3$ (from 0.0 to 0.50 mole equivalents), were examined by nmr (100.1 MHz). With the aid of decoupling experiments, complete proton assignment in the spectra was possible. Plotting of the resulting proton chemical shifts (τ) versus the number of mole equivalents of shift reagent (C) gave good linear graphs for $C \leq 0.3$. For higher values of C, the chemical shifts slowly approached saturation. A similar experiment was carried out with 279. Table 11 lists the slopes of the linear plots ($0 \leq C \leq 0.3$) of the two bridging protons, H_{9A} and H_{9B}, in the two compounds.*

7

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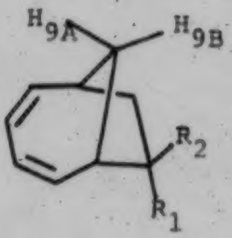
*The shapes of the nmr absorptions for the bridging protons in 263, 271, 274, 275, and 279 are very similar. The high-field proton is seen as a ~~doublet;~~ the low-field proton as a doublet of triplets. There are only small differences in the coupling constants among the compounds.

Table 11: Effect of Eu(fod)$_3$ on the Chemical Shifts of the Bridging Protons in 274 and 279



274: R_1=H, R_2=OH

279: R_1=OH, R_2=H

	Δτ/C	
Cmpd.	H_{9A}	H_{9B}
274	-9.3 ± 0.3	-18 ± 2[a]
279	-5.6 ± 0.1	-6.2 ± 0.1

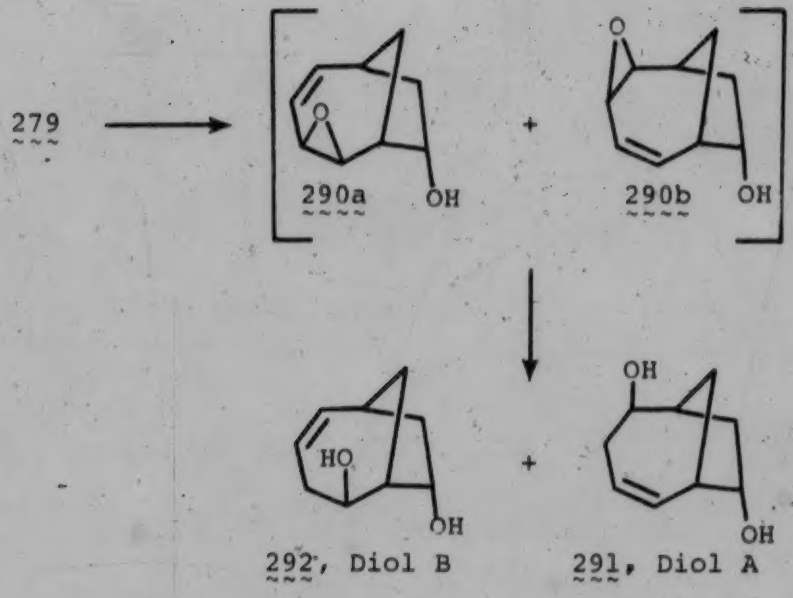
a) The larger error associated with the slope for H_{9B} in 274 arises from some uncertainty in the exact chemical shift of H_{9B} in the various spectra.

The doublet in 275 has been attributed to the proton syn to the diene moiety (vide supra). Extending this conclusion, we ascribed the doublet in the spectra of 274 and 279 to H_{9A}.

Whereas the slopes for the bridging protons in **279** are approximately the same, this is not the case in **274**. One of the bridging protons travels downfield twice as fast as the other. This behaviour is just the expected for the *endo* alcohol and the *exo* alcohol respectively.

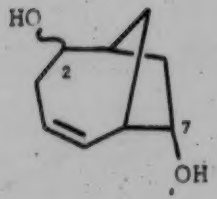
As discussed earlier in Chapter 7, allylic epoxides are often unstable substances to work with. To avoid this added complication in the epoxidation study of **279**, we chose to reduce directly the crude epoxide mixture with lithium aluminum hydride and then to analyse the resulting diols. A methylene chloride solution, equimolar in *endo* alcohol **279** and *m*-chloroperbenzoic acid, was stirred at 0° for 5-7 hr and esterified with ethereal diazomethane. The allylic epoxides were reduced with lithium aluminum hydride. After work-up, glpc (Carbowax 20m) of the crude diols indicated the presence of compounds A and B, in approximately a 60:40 ratio, in addition to *m*-chlorophenylmethanol. A sample of each product was obtained 80-90% pure by column chromatography (silicic acid).

Structures for the two diols that we considered possible are shown below, labelled **291**-**300**. Compounds **295**-**298** would result from a 1,4-addition of hydride to the intermediate allylic epoxides. Compounds **299** and **300** were



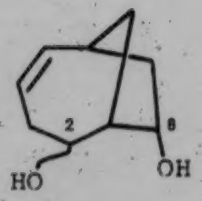
included as the products arising from a possible intramolecular reduction step (see **301**). Although the oxirane would be opened by addition of hydride to the electronically less favoured carbon, the steric ease of such an intramolecular process may override electronic aspects. Lithium aluminum hydride reduction of the *exo* epoxide of **282** gave **302** in good yield.[127]

On the evidence provided by spectroscopic and chemical studies, the diols have been assigned the structures **291** and **292**. The diol with the shorter glpc (Carbowax 20m) retention time (*i.e.* diol A) corresponds to the 1,4-diol, **291**. These studies are described throughout the remainder of this chapter.



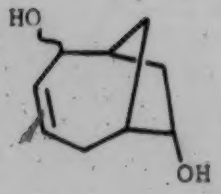
291 (exo)

293 (endo)



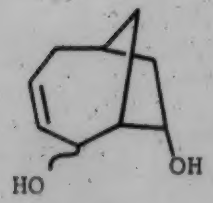
292 (exo)

294 (endo)



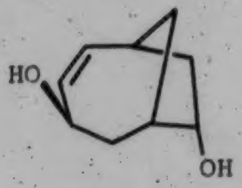
295 (exo)

296 (endo)

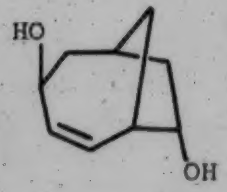


297 (exo)

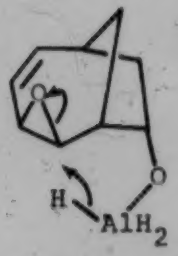
298 (endo)



299



300



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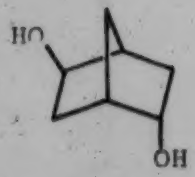


302

Table 12 summarizes some decoupling experiments performed on diol A (ca. 90% pure). The close similarity of the chemical shifts ($CDCl_3$) and multiplicities of H_7 in 279 and 283 and of the doublet of triplets at τ 5.70 in diol A strongly suggested that this absorption belongs to

Table 12: Nmr Analysis (100.1 MHz, $CDCl_3$) of Diol A (**291**)

Proton Irrad'd	Chemical Shift (τ) and Multiplicity[a] (Hz)				
	$H_{4,5}$	H_7	H_2	H_6	H_{3A} and/or H_{3B}
	4.26 m	5.70 d,8.7 t,6.6	6.04 d,5.5 t,3.5	7.19 bq	ca. 7.50 (obscured)
$H_{4,5}$		--	--	bt	**
H_7				bt	**[b]
H_2	--			--	**
H_{3A} and/or H_{3B}	**	*[c]	bs		

a) For an explanation of the multiplicity abbreviations, see page 204, Chapter 10.

b) H_{3A} and H_{3B} are two protons of a broad five-proton absorption. The change in the τ 7.50 region is caused by the presence of H_{8A} and/or H_{8B}.

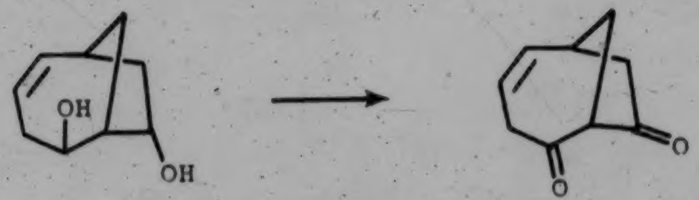
c) Irradiation at τ 7.50 causes partial decoupling of H_{8A} and/or H_{8B}. A decrease in the coupling constants of the H_7 signal is observed.

the proton geminal to the hydroxyl in the cyclopentane ring. Furthermore the hydrogenation **279**→**283** produced only

	Compound **279**	Compound **283**
H_7	5.60	5.70
	d,8.7 Hz	cd,*ca*.9 Hz
	t,6.5 Hz	t,*ca*.7 Hz

a small up-field shift of H_7. There is no reason to suspect that a much larger shift to τ 6.04 should occur in the diol. Irradiation of the olefinic protons or of the signal at τ 5.70 collapses the isolated one-proton absorption at τ 7.19 to a broad triplet. The latter signal is therefore attributed to an allylic bridgehead proton adjacent to CHOH (cyclopentane ring), thus ruling out all diol possibilities except **291**, **293**, and **300**. In addition, irradiation of the olefinic protons has no effect on the methine absorption at τ 6.04 (CH-OH in the cycloheptane ring) but strongly affects the region near τ 7.50, characteristic for an allylic methylene group. Finally, decoupling the signals at τ 7.50 collapses the seven-membered ring CH-OH to an ill-defined singlet. The data are consistent only with the C_2 epimers **291** and **293**.

The nmr spectrum of diol B (*ca*. 80% pure) is much less informative, mainly because neither of the two bridgehead protons appears as an isolated signal. To ascertain whether the hydroxyl group in the seven-membered ring was allylic or not, a sample of the diol (*ca*. 75% pure, contaminated with diol A and *ca*. 10% of other products) was oxidized at 0° with two equivalents of Jones' reagent. The ir spectrum (CCl_4) of the crude dione contains only two bands in the carbonyl region, at 1745 cm^{-1} (strong) and at 1707 cm^{-1} (strong). The uv spectrum (cyclohexane) provides further evidence for the absence of an α,β-unsaturated ketone. The olefin chromophore appears as

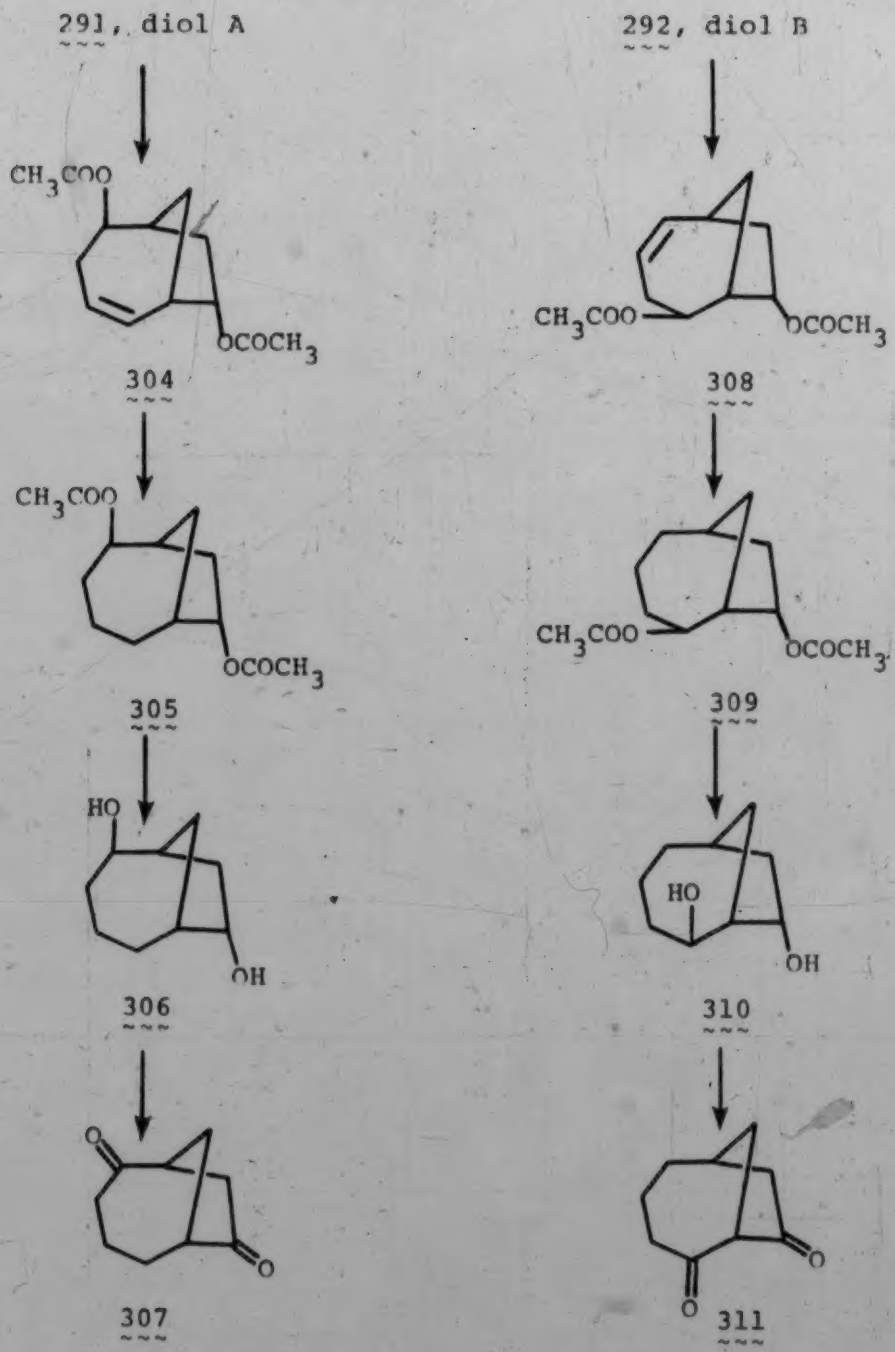


292, diol B

303

only end absorption (λ_{max}<210 nm) and the carbonyl group exhibits a maximum at 299 nm (ε=*ca*.20). The reaction products were not further characterized. The data seems incompatible with all diol structures but **291**, **292**, **293** and **294**. That the two diols were not epimers (*i.e*. **291** and **293**) was proved by the conversion of the diols into two different saturated diketones, **307** and **311**. A second purpose for performing the sequence of reactions outlined in Scheme 11 was to obtain samples of the saturated diols **306** and **310** for further study (*vide infra*).

Scheme 11

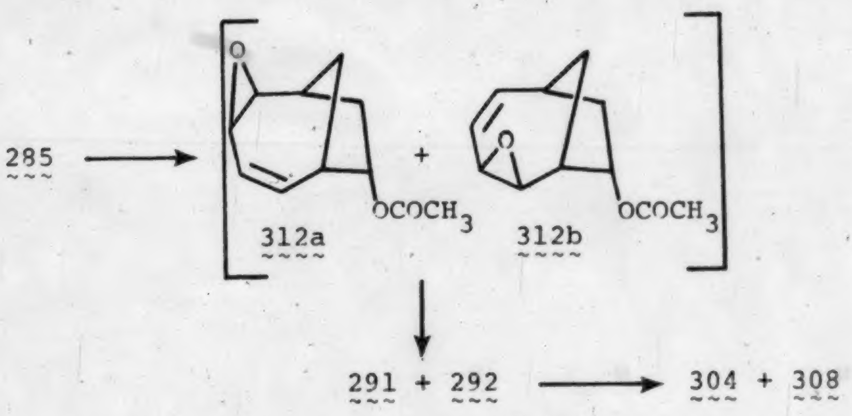

291, diol A
292, diol B
CH$_3$COO
OCOCH$_3$
304
CH$_3$COO
OCOCH$_3$
308
CH$_3$COO
OCOCH$_3$
305
CH$_3$COO
OCOCH$_3$
309
HO
OH
306
HO
OH
310
O
O
307
O
O
311

Because of the complications that arose in the hydrogenation of **279**, the diols A and B were first converted to their diacetates **304** and **308**, using acetic anhydride and pyridine. Hydrogenation (PtO_2 catalyst) of the diacetates in ethyl acetate and subsequent removal (hot methanolic sodium methoxide) of the acetyl groups led to **306** and **310**. Jones' oxidation converted each smoothly into the corresponding diketones **307** and **311**. All reactions proceeded cleanly in high yield and spectral data (ir and nmr) are consistent with each of the compounds. Glpc analysis (UCW-98) demonstrated that the saturated diketones are different. To summarize then, diol A is either **291** or **293** and diol B is likely **292** or **294**.

At low concentrations (0.0019 *M*), the ir spectrum (CCl_4) of diol A shows an intramolecularly bonded OH band at 3568 cm^{-1} as well as a free OH band at 3626 cm^{-1}. The former absorption is presumably due to the presence of the double bond since the high dilution ir spectrum of **306** shows only a free OH peak.

The high dilution (0.0033 *M*) ir spectrum (CCl_4) of diol B does not contain an intramolecular OH band. Because of its geometry we believed that compound **294** would possess strong intramolecular bonding. Accordingly, we strongly favoured structure **292** for diol B.

For additional information concerning the orientation of the hydroxy group in the seven-membered rings of diols A and B, the epoxidation of the endo acetate 285 was examined. With the acetoxy group, only steric factors should control the direction of peracid attack. One mole equivalent of m-chloroperbenzoic acid and 285, dissolved in methylene chloride, was stirred at 0° for 8 hr and esterified with ethereal diazomethane. Reduction of the crude epoxy acetates with lithium aluminum hydride gave, after work-up, a mixture of chiefly two diols (glpc, Carbowax 20m). A pure sample of the diacetate of each product was obtained by two methods. Conversion of the crude diol mixture to the corresponding diacetates followed by preparative glpc (Reoplex) yielded each diacetate as a solid compound. After two recrystallizations both diacetates were analytically pure. The 1,4-derivative melted at 76.3-77.2°, the 1,3-derivative at 56.2-57.2°. The



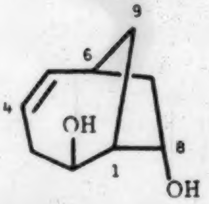
alternative method involved first column chromatography of the diols on silicic acid. Appropriate fractions were combined and acetylated. At least three recrystallizations were required to purify completely the crude diacetates. The second method was the less efficient.

Similarly, pure specimens of the 1,4-diacetate 304 (mp 76.0-76.5°) and the 1,3-diacetate 308 (mp 56.0-57.0°) were prepared from the diols derived from the epoxidation of 279.

Each pair of diacetates are identical in spectral properties and glpc behaviour (UCW-98, Reoplex, Carbowax 20m). There is no depression of the mixture melting points. Thus both the *endo* alcohol 279 and the *endo* acetate 285 lead to mixtures containing the same proportions of the same two diols. This result lends additional support for the proposed stereochemistry of the 1,3-diol B and suggests that diol A also likely has an *endo*, *exo* configuration.

With samples of pure diol B now accessible from the hydrolysis of the pure 1,3-diacetate, a reexamination of the nmr spectrum of the diol was undertaken, using a different approach. It was mentioned above that the nmr of diol B is not very informative because the signals for the two bridgehead protons are buried in the absorptions of other protons (see Figure 9). In our experiments with the europium shift reagent and compounds 274 and 279, we had observed very impressive differentiation of chemical shifts, even when the shift reagent was present only in a few percent of a mole equivalent. Just as impressive was the excellent resolution of the signals throughout the experiments. With respect to diol B, it seemed to us quite possible that the bridgehead proton H_1, in the presence of the shift reagent, would be pulled out of the conglomerate absorption at τ 7.4-7.8.

In the presence of only 0.05 mole equivalent of $Eu(fod)_3-d_{30}$, a spectrum ($CDCl_3$) of diol B is obtained from which it is possible to prove unambiguously the homoallylic 1,3-diol constitution of the diol (see Figure 10).



292, diol B

In the shifted spectrum (Figure 10), the H_1 absorption is now visible as a broad quartet. From results of a decoupling study (Table 13), extensive assignment of the spectrum is possible. Only structures 292 and 294 are compatible with the decoupling experiment.

Figure 9: Nmr Spectrum (100.0 MHz; CDCl$_3$) of Diol 292

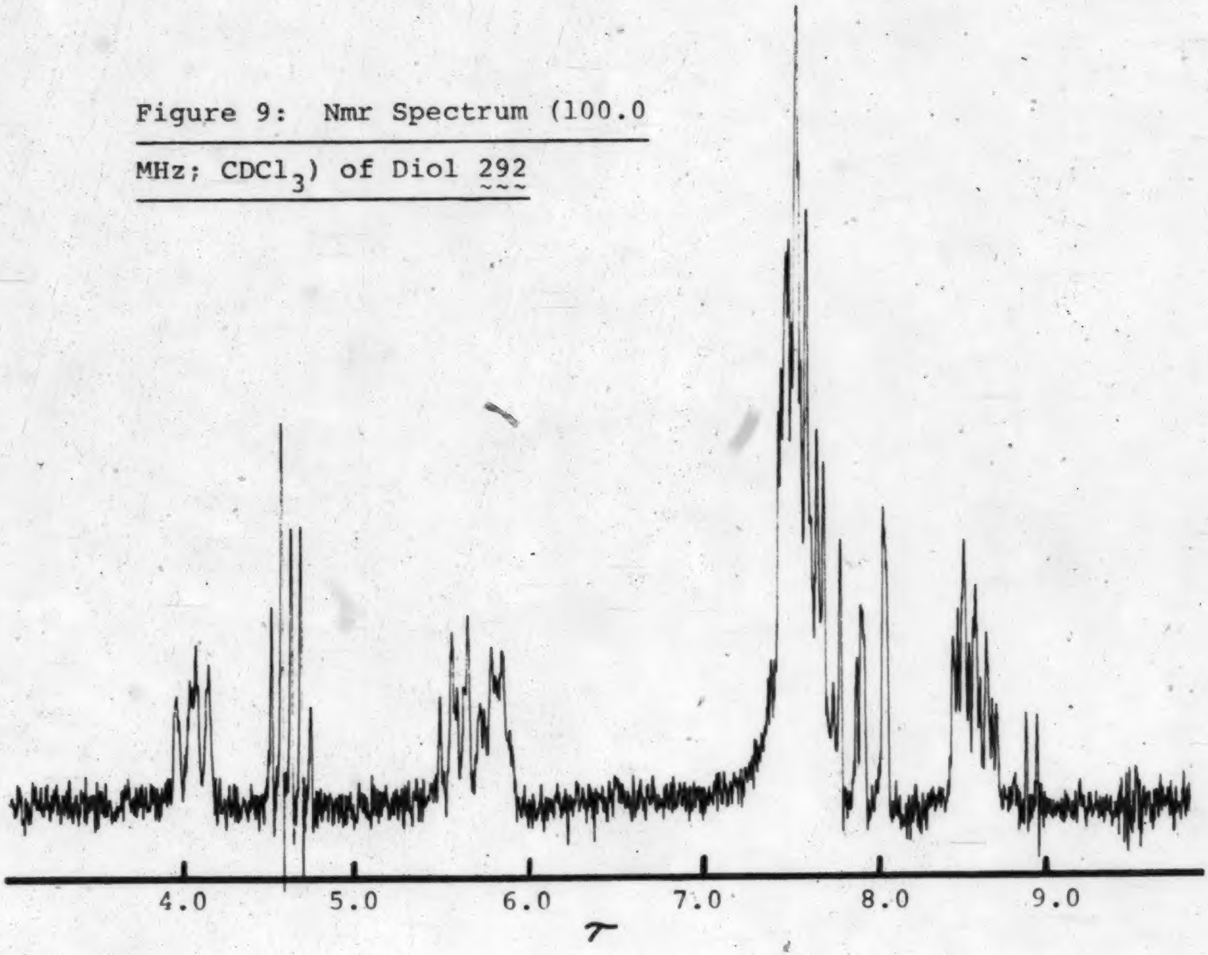


Figure 10: Nmr Spectrum (100.0 MHz; $CDCl_3$) of Diol 292 in the Presence of 0.05 Mole Equivalent $Eu(fod)_3$-d_{30}

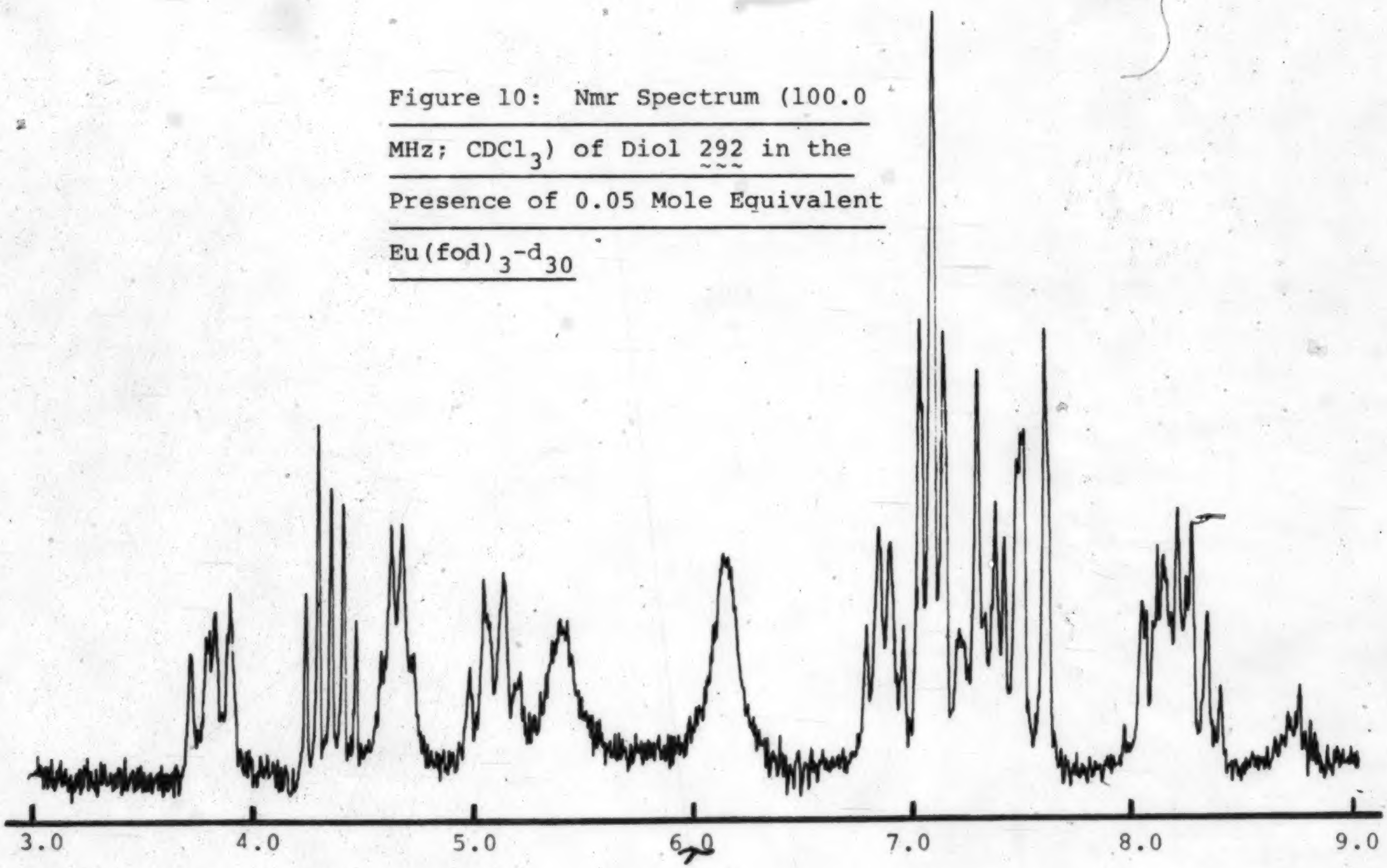


Table 13: Nmr Analysis (100.0 MHz, $CDCl_3$) of Diol B (292) in the Presence of 0.05 Mole Equivalents of $Eu(fod)_3$-d_{30}

Proton	Chemical Shift (τ) and Multiplicity[a,b] (Hz)										
Irrad'd	H_5	H_4	H_2	H_8	H_1	$2H_3$	H_6	H_{7A}	H_{9A}	H_{7B}	H_{9B}
	3.80	4.34	4.65	5.09	6.87	7.08	ca.7.24	ca.7.32	7.54	8.12	8.26
	m	m	bq	d,9 t,6.5	bq	ct,5-6	m	m	cd,12-13	m	d,12 t,3
H_2	--	--			t	cd,5.5	--	--	--	--	--
H_8	--	--			t	--	--	**	--	**	--
H_1	--	--	**	**		--	--	--	--		d,12 d,3
H_5			--	--	--	t,5.5	**	--	--	--	--
H_4					--	cd,5.5	--	--	--	--	--
H_{9B}									bs		

a) For an explanation of the multiplicity abbreviations, see page 204, Chapter 10.

b) Tabulated coupling constants are approximate.

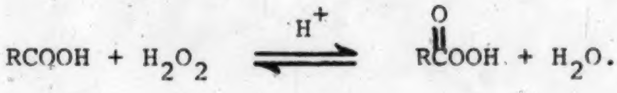
The *exo* configuration at C_2 of diol B was established beyond all doubt in later experiments with the C_2 epimer of diol B (*vide infra*). Therefore approximately 50% of the *m*-chloroperbenzoic acid attacks the Δ^4 double bond of **279** from the *exo* side. It seems impossible to imagine that the two double bonds of the diene system in **279** differ in character enough to cause the other half of the peracid to attack the Δ^2 double bond from the *endo* side. Although we have no direct evidence for the configuration of the C_2-hydroxyl in diol A, we believe that diol A must also have an *endo*, *exo* stereochemistry.

The products from the simple epoxidation of **279** have now been identified. Although the yields of allylic epoxides are very good, neither major product has the required *endo* orientation of the oxirane ring. A method to force an epoxidation to the underside of the bicyclic system is to build a percarboxylic acid unit on to the *endo* hydroxyl of **279**. Then with a proper choice of the added unit and with the proper experimental conditions, the peracid might epoxidize the diene moiety from underneath in an intramolecular process. We are not aware of any reported example of an intramolecular epoxidation.

The peracid unit must be attached to the hydroxyl of **279** by a linkage that can be easily broken later on. This would seem to limit the linkage to an ester.

Because of its reactivity the peracid moiety can only be generated after the linkage to **279** has been formed. The problem then becomes to find a high-yield procedure to prepare peracids in the presence of an ester.

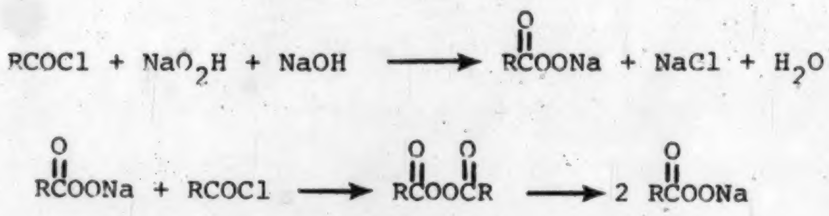
There are two general methods known that produce good yields of aromatic and aliphatic peracids. The synthesis of Silbert *et al.*[131] relies upon the acid-catalysed exchange equilibrium indicated below:



$$RCOOH + H_2O_2 \overset{H^+}{\rightleftharpoons} R\overset{O}{\overset{\|}{C}}OOH + H_2O.$$

The workers used the strong, non-oxidizing acid, methane-sulphonic acid, as both catalyst and solvent. The reaction requires from 1-3 hr and the yields are generally 80-100%.

The second method[132] involves the perhydrolysis of acid chlorides. Perhydrolysis is a classic method to prepare organic peracids but yields were not good until the Japanese chemists found that an excess of base must be used to prevent spontaneous decomposition of the peracid and its anion. Reaction times at 20° are very short

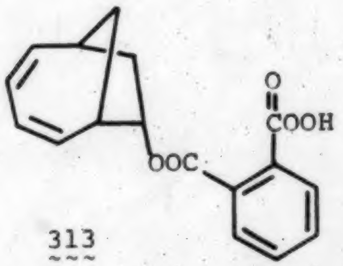


$$RCOCl + NaO_2H + NaOH \longrightarrow R\overset{O}{\overset{\|}{C}}OONa + NaCl + H_2O$$

$$R\overset{O}{\overset{\|}{C}}OONa + RCOCl \longrightarrow R\overset{O}{\overset{\|}{C}}OO\overset{O}{\overset{\|}{C}}R \longrightarrow 2\ R\overset{O}{\overset{\|}{C}}OONa$$

(*ca*. 15 min). The solvent medium is aqueous alcohol or aqueous dioxane and a small amount of magnesium sulphate is added to inhibit the catalytic decomposition of the products by traces of metals.

The use of methanesulphonic acid as solvent is prohibited for our purpose. On the other hand, the low temperature and the speed of the reaction made the perhydrolysis reaction attractive. Under these conditions little saponification of an ester should occur. Since aromatic peracids are more stable than their aliphatic counterparts, the preparation of 313 was attempted.



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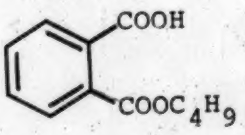

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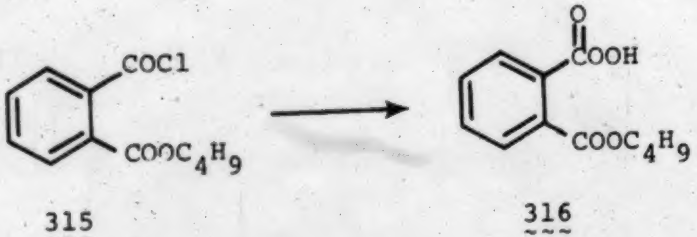
To test the perhydrolysis method, *n*-butyl hydrogen phthalate (314) was converted to its acid chloride (315). Essentially following Ogata and Sawaki's proced-



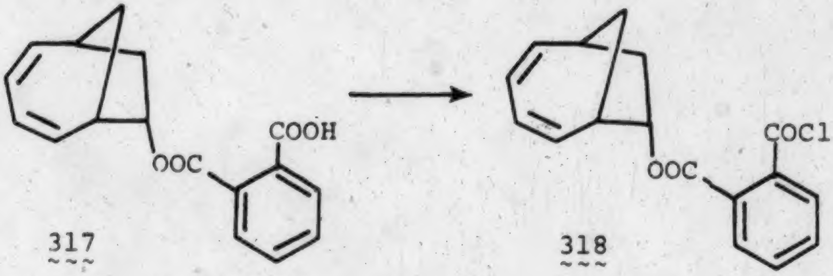
315

316

ure,[132] the acid chloride was then added dropwise to a cold (5°), aqueous dioxane solution containing three mole equivalents of sodium hydroperoxide and a small amount of magnesium sulphate. After 12 min stirring at 7-10°, the reaction was worked up. Analysis of a chloroform solution of the product showed that the peracid **316** had been formed in 84% yield. No evidence of hydrolysis of the ester was observed by glpc (UCW-98) and nmr spectroscopy of the esterified (diazomethane) crude product.

Although the yield of **316** is excellent, the experimental procedure is not well suited for the preparation of **313**. The main drawback is the high concentrations of reagents that are employed. For example, the acid chloride is added neat to the aqueous solution. When the reaction **315**→**316** was repeated but using modified procedures that we considered applicable to the synthesis of **313**, the yields of **316** dropped only to 70-75%.

Compound **313** was prepared in the following way. In the presence of phthalic anhydride and pyridine the *endo* alcohol **279** was converted quantitatively to the half phthalate ester **317**. The required acid chloride **318** was made via the potassium salt of **317**. Thus **317** was neutralized with one equivalent of potassium *tert*-butoxide in tetrahydrofuran. Reaction then with oxalyl chloride led cleanly to **318**.

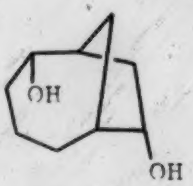


317 318

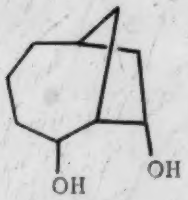
To date the preparations of 313 from 318 have produced products derived mainly from intermolecular rather than intramolecular epoxidations. The products were analysed by reducing the esterified (diazomethane) mixture of allylic epoxides with lithium aluminum hydride. After removal of o-dihydroxymethylbenzene by chromatography, the crude product consisted mainly of two diols. These diols were shown to be the previously isolated diols 291 and 292. The diols were purified as their diacetates in the manner described before. In mixture, the pure diacetates (mp 76.2-77.0°, 56.0-56.8°) did not depress the melting points of 291 and 292.

Although we have not yet succeeded to force the formation of the endo epoxides by this method, we are optimistic and believe that it is at present solely a technical problem. With the development of a practical method to effect intramolecular epoxidations, some very interesting synthetic and mechanistic studies will be possible.

To help simplify future investigations on this problem, the synthesis of the authentic endo, endo diols 319 and 320 has been started. With the four diols, 306,



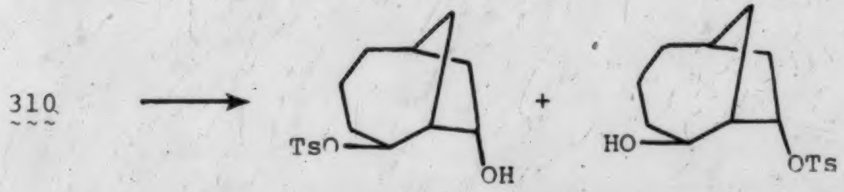
319



320

310, 319, and 320 on hand, a quantitative analysis of the epoxidation mixtures becomes possible using glpc. (A capillary column would probably be necessary for this work.) In this way the laborious separation and purification of the isomers would be avoided.

The synthesis of 320 has been completed. The reaction of equimolar quantities of pure 310 (prepared from purified 308) and p-toluenesulphonyl chloride in the presence of pyridine gave a mixture of the two possible monotosylates in which 321 predominated. Chromatography of the mixture on silicic acid gave a sample of

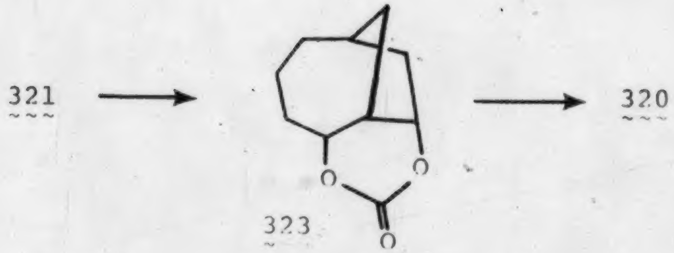


321

322

321 that was ca. 90% pure by nmr spectroscopy. Compounds 321 and 322 were easily distinguished by their nmr spectra. A proton geminal to a hydroxyl group in the monotosylate believed to be 321 had a chemical shift and multiplicity essentially the same as the protons geminal to the cyclopentyl hydroxyl groups in 279, 291, 292, and 306. Furthermore, Jones' oxidation of the monotosylate gave a product that exhibited a single carbonyl stretching band in the ir spectrum at 1738 cm^{-1}.

Corey and Terashima[133] recently reported that tetrabutylammonium formate is an excellent reagent to use for S_N2 displacement reactions of tosyloxy groups. Tetrabutylammonium formate was prepared by us from the corresponding ammonium iodide. Passing an aqueous solution of the iodide through an anion exchange column (Dowex 1-X8 in the hydroxide form) yielded tetrabutylammonium hydroxide which was then neutralized with one equivalent of formic acid. The bulk of the water was removed under reduced pressure at 30° and the product was dried[134] by azeotropic distillation using benzene. A crystalline solid remained which was then recrystallized three times from dry, purified acetone. Reaction of the purified ammonium salt with 321 at room temperature was complete in 2 hr. An excellent yield (>90%) of the cyclic carbonate 323 was obtained.



323

The structure of **323** is firmly established by the combined evidence of ir and nmr spectroscopy and chemical ionization mass spectrometry. No formate proton is present in the nmr spectrum but the ir spectrum ($CHCl_3$) contains a strong carbonyl band at 1738 cm^{-1}. The chemical ionization mass spectrum, recorded using methane as the reactant gas, displays a (P+1) peak at _m/e_ 183. With ammonia as the reactant gas, the spectrum exhibits peaks at _m/e_ 200 (P+18) and at _m/e_ 183 (P+1).

The probable explanation for the oxidation product **323** is that the tetrabutylammonium formate was oxidized to tetrabutylammonium bicarbonate during the azeotropic drying. The benzene had not been distilled under a nitrogen atmosphere.

The unexpected carbonate proved that the molecule now possessed _endo_ substituents at both C_2 and C_8. Treatment of the carbonate with methanolic sodium methoxide gave the desired diol **320**. Spectral data are consistent with the assigned structure. The characteristic doublet of triplets for the methine proton geminal to the cyclopentane hydroxyl is seen at τ 5.52. The ir spectrum (CCl_4) of a dilute solution (*ca*. 0.003 *M*) of **320** exhibits medium OH bands at 3636 cm^{-1} and 3624 cm^{-1} and a strong band at 3548 cm^{-1}.

Further work on this project must be left in the hands of others.

CHAPTER 9

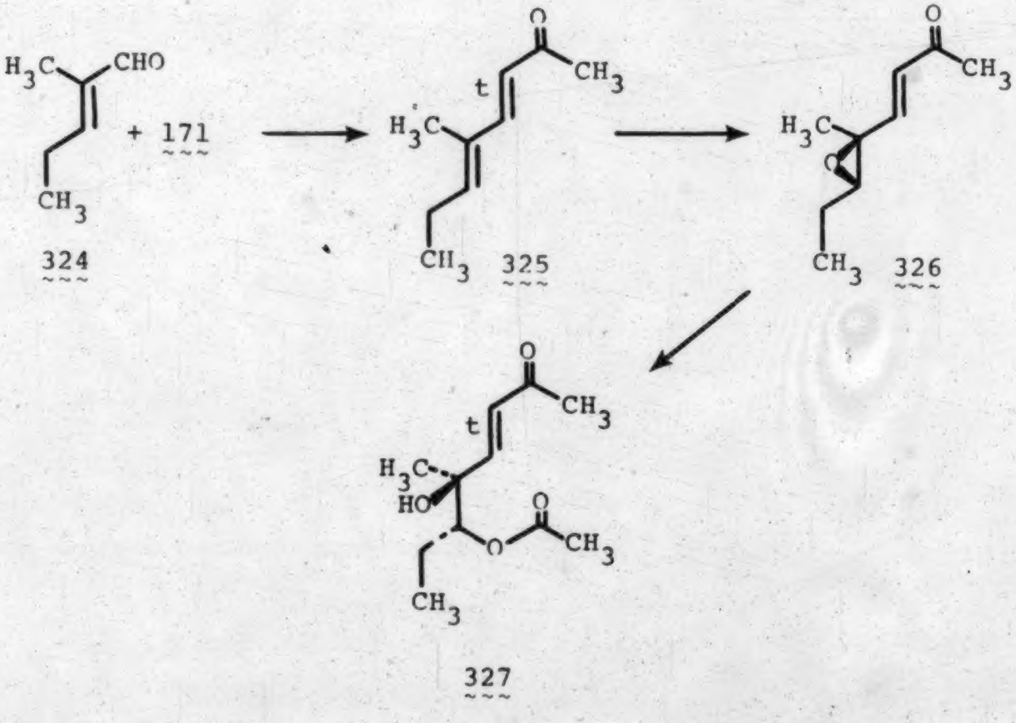
METHYNOLIDE--THE PRESENT STAGE OF ITS SYNTHESIS

In the discussion of results reported in this thesis, mention has been made to contributions by Drs. Kim, Spessard, Davis and Yamamoto. This chapter describes additional work performed by Drs. Spessard, Yamamoto, and Rossy.

The Left Side of Methynolide

At the end of Chapter 5 compound **140** was proposed as a potential precursor to methynolide. From **140**, completion of the synthesis involves the intramolecular opening of the C_{10},C_{11}-oxirane by the carboxy group, followed by the removal of any protecting groups that may be present. Dr. Spessard carried out a series of model experiments designed to assess the feasibility of this approach. The test compound for this study was the γ,δ-epoxy-α,β-unsaturated ketone **326**.

The synthesis of **326** started from 2-methyl-2-pentenal (**324**), the aldol self-condensation product of propanal. Although this aldol product has been known for almost one hundred years, it was not until recently that the stereochemistry of the double bond was conclusively established as indicated in structure **324**.[135a] Acetylmethylenetriphenylphosphorane (**171**) was condensed with **324**, prepared by the method of Evans *et al.*,[135b] to give the dienone **325**. Treatment of **325** with *m*-chloroperbenzoic acid resulted in epoxidation exclusively at the γ,δ-double

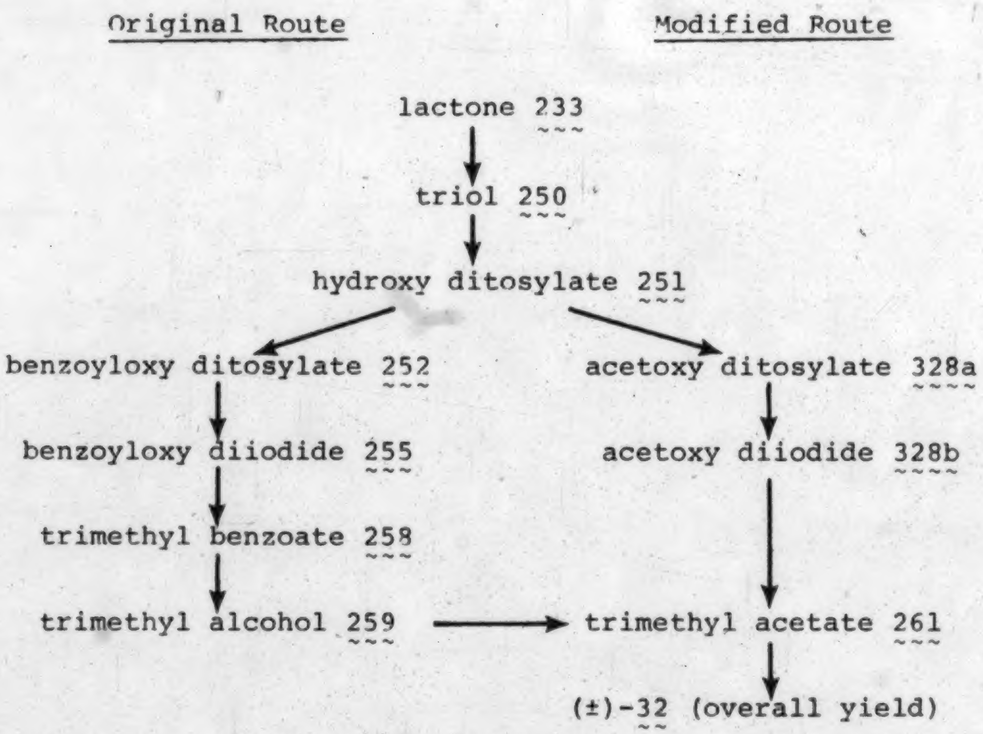

H3C
CHO
+ 171
CH3
324
O
CH3
t
H3C
CH3
325
O
CH3
H3C
O
CH3
326
O
CH3
t
H3C
HO
O
O
CH3
CH3
327

bond.

When the epoxide **326** was stirred in hot acetic acid, the oxirane was cleaved in the manner desired. Compound **327** contains all the stereochemical features present in the C_7-C_{13} fragment of methynolide.

Further Work with the Lactonic Acid (±)-**32**

(i) By modifying slightly the previously outlined reaction scheme (see Chapter 7) for the conversion of the lactone **233** to the trimethylcycloheptenyl acetate **261**, Dr. Yamamoto has been able to improve the overall yield of (±)-**32**. One advantage of the modified procedure

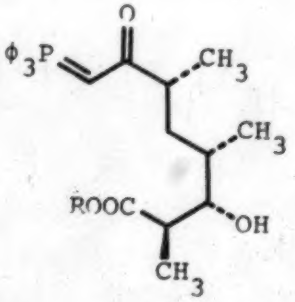

Original Route
Modified Route
lactone 233
triol 250
hydroxy ditosylate 251
benzoyloxy ditosylate 252
benzoyloxy diiodide 255
trimethyl benzoate 258
trimethyl alcohol 259
acetoxy ditosylate 328a
acetoxy diiodide 328b
trimethyl acetate 261
(±)-32 (overall yield)

Original Route: 23%

Modified Route: 30%

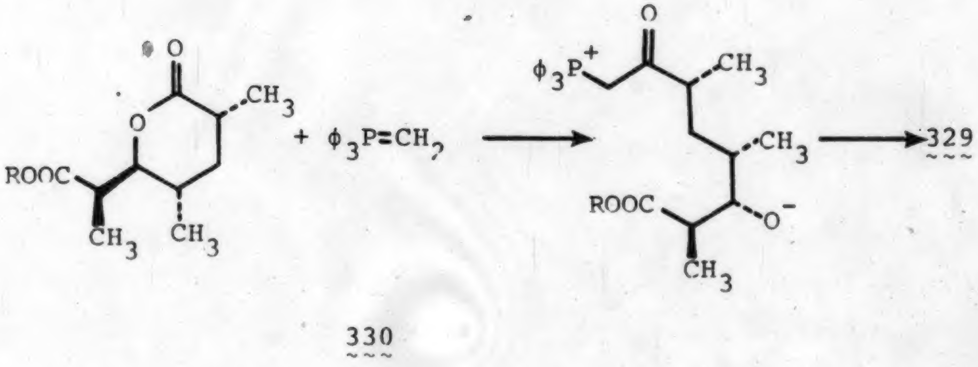
is that the acetoxy ditosylate **328a** is obtained as a crystalline substance. The crude 328a is isolated in 84% overall yield from lactone 233. One recrystallization affords analytically pure material.

(ii) If the results of Dr. Spessard's study of 326 are to be applied in the synthesis of methynolide, then the preparation of the stabilized phosphorane 329 becomes necessary.



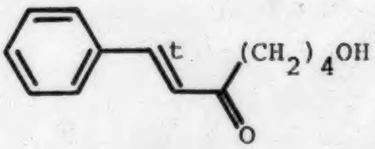
329

The synthesis of this compound is presently being developed. Encouraging preliminary results have been obtained. Drs. Yamamoto and Rossy have shown that in the presence of one equivalent of aqueous sodium hydroxide, the lactone moiety of (±)-32 is quantitatively saponified. The methyl ester remains unaltered. If this selectivity is applicable to other nucleophilic reactions on (±)32, then a one-step synthesis of 329 appears possible by using methylenetriphenylphosphorane (330). Reactions of 330


ROOC
CH3
CH3
+ ϕ3P=CH2
ϕ3P+
O
O-
ROOC
329

330

with simple esters are known.[136] Dr. Rossy has shown that the above reaction proceeds in a test case with valerolactone. Condensation of the crude product with benzaldehyde



331

gives the expected olefin 331.

CHAPTER 10

EXPERIMENTAL

All melting and boiling points are uncorrected.

The ir spectra were obtained on Perkin-Elmer model 21 and 257 infrared spectrometers. In reported ir spectral data the following abbreviations are used: s, strong absorption; m, medium absorption; w, weak absorption; b, broad absorption; sh, shoulder absorption.

The mass spectra were obtained on A.E.I. MS-2, MS-9, and MS-12 spectrometers.

The nmr spectra were recorded on Varian Associates A-60 and HA-100 spectrometers. In reporting nmr data the following abbreviations are used: m, multiplet; s, singlet; d, doublet; t, triplet; q, quartet. The abbreviation b (broad) may prefix one of the above multiplicity abbreviations, in which case the specified multiplicity is just intended to give a visual picture of the absorption with no strong suggestion as to the true nature of the splitting pattern. The abbreviation c (complex) may prefix a multiplicity abbreviation. This prefix is used to indicate the presence of one or more small coupling constants (J<2Hz). In reporting the results of decoupling experiments in the preceding chapters, the symbol "**" indicates that the appearance of an absorption has been strongly altered. The symbol "*" is used for describing absorptions that undergo only small changes in shape.

Analytical glpc were performed on a F&M model 5750 research chromatograph, equipped with 6 ft x 3/16 in columns and a flame ionization detector. Preparative glpc were carried out on a F&M model 700 chromatograph, equipped with 10 ft x 1/4 in. columns.

All reactions were conducted under a dry nitrogen atmosphere unless otherwise stated.

4-Phenylbutanoyl Chloride (147)

To a cold (5°), stirred mixture of 4-phenylbutanoic acid (7.50 g; 45.7 mM) and freshly distilled thionyl chloride (6.50 g; 54.6 mM) was added N,N-dimethylformamide (15 mg; 0.20 mM). The reaction was protected from atmospheric moisture with a Drierite drying tube. After the vigorous evolution of gases had subsided, the solution was heated at 90° for 15 min. Excess thionyl chloride and the small amount of N,N-dimethylformamide were then removed by distillation under reduced pressure. Final distillation of the dark residue gave 147 as a colourless liquid (bp 110-111° at 7 torr; lit.[137] 119° at 9 torr).

Yield: 7.32 g; 88%.

ir ($CHCl_3$): 1800 cm^{-1} (s); 1730 (m); 1605 (m); 1497 (m);
1457 (m); 1404 (m).

1-Bromo-5-phenyl-2-pentanone (**149**)

A solution of **147** (6.98 g; 38.2 mM) in dry ether (100 ml) was added dropwise over 1.5 hr to a cold (0°), stirred ethereal solution (240 ml; 0.50 *M*; 120 mM) of diazomethane under nitrogen. After stirring for 30 min at I0°, the yellow solution was stirred an additional 3.5 hr at room temperature. The yellow diazoketone **148** remained as an oil in the flask after the solvent and excess diazomethane had been removed under reduced pressure at room temperature.

The diazoketone was the diluted with dry tetrahydrofuran (50 ml), cooled to 0°, and decomposed by the dropwise addition of 48% aqueous hydrobromic acid (*ca.* 5.5 ml; 42 mM HBr). Nitrogen evolution ceased before addition was complete. After addition, the solution tested acidic. The yellow solution was stirred 1.0 hr at room temperature, poured into water (400 ml), and extracted with ether (4 x 100 ml). The combined extract was washed to neutrality with water (2 x 100 ml), concentrated to an oil, diluted with methylene chloride (150 ml), dried (anhydr. Na_2SO_4), and reconcentrated to a yellow-orange oil (ca. 86% 149 and 14% 150).

Yield: 8.06 g; 88%.

ir (film): 1732 and 1717 cm^{-1} (s); 1601 (m); 1494 (m); 1453 (m); 747 (s); 697 (s).

nmr ($CDCl_3$): τ 2.79 (bs, 5H); 6.25 (s, 2H); 7.17-7.76 (m, 4H); 7.80-8.40 (m, 2H); 6.07 (s, $COC\underline{H}_2Cl$).

mass spectrum: calcd. mass for $C_{11}H_{13}{}^{79}BrO$: 240.0149.
meas. m/e: 240.0153.

2-Oxo-5-phenylpentyltriphenylphosphonium Bromide (151)

A solution of triphenylphosphine (9.26 g; 35.4 mM) in benzene (30 ml) and a solution of 149 (7.80 g containing 14% 150; 32.4 mM) in benzene (20 ml) were mixed under nitrogen at room temperature. After 30 sec, a white precipitate formed. The mixture, after stirring overnight, was filtered and the precipitate was triturated with hot benzene (2 x 150 ml) and freed of solvent (room temperature, 0.1 torr). The crude phosphonium bromide (ca. 11 g) was finally recrystallized from ethyl acetate--methanol (mp 210.0-211.0°).

Yield: 10.64 g; 65%.

ir ($CHCl_3$): 2905 cm^{-1} (s); 1712 (s); 1441 (s); 1108 (s).

nmr ($CDCl_3$): τ 1.80-2.62 (m, 15H); 2.84 (bs, 5H); 4.09 (bd, J=12Hz); 6.76-7.23 (m, 2H); 7.25-7.70 (m, 2H); 7.83-8.50 (m, 2H).

mass spectrum: meas. *m/e* 423 (P-Br).

2-Oxo-5-phenylpentylidenetriphenylphosphorane (**145**)

The phosphonium bromide **151** (9.40 g; 18.7 mM) was added in portions over 30 min to a vigorously stirred mixture of aqueous potassium carbonate (10% by wt; 400 ml) and benzene (100 ml). The mixture was stirred overnight, the benzene layer was decanted, and the aqueous layer was extracted with benzene (3 x 100 ml). The combined benzene solutions were washed with water (3 x 100 ml) and with saturated aqueous sodium chloride solution (100 ml) and dried (anhydr. Na_2SO_4). Removal of the solvent gave **145** as a yellow oil. All attempts to crystallize the oil failed. During these attempts, the oil darkened appreciably. The bulk of the coloured impurities were successfully removed by filtering a methylene chloride solution of **145** through a column of neutral alumina (activity II; 400 g). Again removal of the solvent afforded a yellow oil.

Yield: *ca.* 6.5 g; 82%.

ir ($CHCl_3$): 1524 cm^{-1} (s); 1439 (s); 1400 (s); 1104 (s);

874 (s).

nmr ($CDCl_3$): τ 2.00-3.15 (m, 20H); 6.35 (bs, 1H); 7.10-8.50 (m. 6H).

mass spectrum: calc. mass for $C_{29}H_{27}OP$: 422.1800.
meas. *m/e*: 422.1815.

Preparation of Benzoyl Chloride in the Presence of 1-Vinylcyclohexyl Acetate (153)

A solution of benzoic acid (0.110 g; 0.90 mM) in dry benzene (3 ml), maintained under a dry nitrogen atmosphere, was treated at 5° with a hexane solution of *n*-butyllithium (1.30 *M*; 0.69 ml; 0.90 mM). 1-Vinylcyclohexyl acetate (105 mg; 0.624 mM) and dry pyridine (*ca*. 7 mg; 0.09 mM) were then added. To the vigorously stirred, cold (5°) mixture was added, by syringe over *ca*. 3 min, distilled oxalyl chloride (0.30 ml, 3.5 mM). During the addition the tip of the syringe needle was submerged in the mixture. After stirring 2 hr, the mixture was diluted with carbon tetrachloride (3 ml) and centrifuged. The clear centrifugate was concentrated to an oil. The nmr spectrum and glpc (UCW-98) showed the product to consist solely of benzoyl chloride and **153**.

2-(1,3-Dithian-2-yl)-2-propanol (156)

A hexane solution of *n*-butyllithium (72 ml; 1.60 *M*; 115 mM) was added via syringe, at a rate of *ca*. 5 ml/min, to a cold (-30°), stirred solution of 1,3-dithiane (15.0 g; 125 mM) in dry tetrahydrofuran (400 ml) under nitrogen. After 2 hr stirring, the clear solution of 2-lithio-1,3-dithiane, maintained at -30°, was treated dropwise with dry acetone (8.57 ml, 116 mM). Stirring was continued for 6 hr at -15°, then for 20 hr at 0°. Following concentration to *ca*. 100 ml, the reaction mixture was diluted with water (100 ml), neutralized to pH 7.5 with aqueous hydrochloric acid (1.0 *M*), and extracted with ether (4 x 80 ml). The combined extract was washed with saturated sodium chloride solution, concentrated to an oily residue, diluted with methylene chloride (150 ml), and dried (anhydr. Na_2SO_4). Evaporation of the solvent gave crude 156 as a yellow oil. Fractional distillation removed the small amount (*ca*. 1.0 g) of 1,3-dithiane contained in the crude product. The distilled 156 (bp 83° at 0.03 torr) crystallized readily at room temperature. mp 39.6-40.0°; recrystallized from pentane.

Yield: 15.6 g; 76%.

ir ($CHCl_3$): 3500 cm^{-1} (bm); 1388 and 1375 (s); 1336 (s);

1152 (s); 917 (s); 899 (m).

nmr ($CDCl_3$): τ 5.84 (s, 1H), 6.95-7.25 (m, 4H), 7.63 (s, 1H); 7.80-8.40 (m, 2H); 8.64 (s, 6H).

2-(1,3-Dithian-2-yl)-2-propyl Acetate (157)

The hydroxy dithiane 156 (14.50 g; 81.4 mM) was dissolved in freshly distilled isopropenyl acetate (100 ml) which contained p-toluenesulphonic acid monohydrate (1.0 g, 5.25 mM) and the solution was heated under nitrogen at 60° for 24 hr. The cooled dark liquid, which contained an immiscible oil, was neutralized with pyridine, stripped of isopropenyl acetate under reduced pressure, diluted with benzene (300 ml), and again concentrated to an oil. The residue, dissolved in methylene chloride (150 ml), was washed with aqueous sodium bicarbonate (5% by wt, 4 x 50 ml), water (100 ml), aqueous hydrochloric acid (1.0 M, 4 x 50 ml), and with water (100 ml) and finally was dried (anhydr. Na_2SO_4). Removal of solvent left an orange product which was distilled to give 157 as a white solid. bp 78° at 0.25 torr. mp 68.4-69.7°, recrystallized from pentane.

Yield: 17.21 g; 96%.

ir ($CHCl_3$): 1733 cm^{-1} (s); 1388 (m); 1372 (s); 1253 (bs), 909 (m).

nmr ($CDCl_3$): τ 4.97 (s, 1H); 6.92-7.50 (m, 4H); 7.99 (s, 3H); 7.70-8.34 (m, 2H); 8.43 (s, 6H).

α-Acetoxyisobutyraldehyde (**154**)

A solution of mercuric chloride (4.1 g; 15 mM) in acetone (10 ml) was introduced dropwise into a vigorously stirred mixture of **157** (2.65 g; 12.0 mM) and freshly prepared cadmium carbonate (4.1 g; 24 mM) in acetone (80 ml and water (10 ml), maintained at room temperature and under nitrogen. After the mixture had been stirred for 6 hr at room temperature and for 6 hr at 40°, the mixture was treated with additional cadmium carbonate (2.5 g; 14 mM) and mercuric chloride (2.5 g; 9.2 mM; dissolved in 10 ml acetone). Stirring was continued at 40° for 20 hr and finally at reflux for 30 hr. The cooled mixture was filtered and the solids were washed with acetone. The combined filtrate and washings was concentrated, in the presence of fresh cadmium carbonate, to 10-15 ml by spinning-band distillation. The pot residue was centrifuged and the clear centrifugate was diluted with chloroform (15 ml). After removal of the precipitated solids by centrifugation, the solution was flash-distilled under reduced pressure from the remaining dissolved mercury salts. By glpc analysis (UCW-98), the main product in the distillate was **154**.

However, at least five minor products as well as a significant amount of 157 were also present. Fractional distillation under reduced pressure afforded 154 (ca. 90% purity). For spectral characterization, a sample of pure 154 was obtained by preparative glpc (SE-30, 118°).

Yield: ca. 620 mg; 40%.

ir (film): 1739 cm^{-1} (s); 1390 (m); 1372 (s); 1256 (bs); 1143 (s).

nmr ($CDCl_3$): τ 0.48 (s, 1H); 7.91 (s, 3H); 8.60 (s, 6H).

1-Vinylcyclohexanol (158)

The preparation of 158 was similar to that described in reference 138. Thus a three-necked flask (500 ml), equipped with an overhead stirrer and a dry ice--acetone condenser, was charged with pulverized magnesium turnings (8.02 g, 330 mM). The system was thoroughly dried and maintained under an atmosphere of nitrogen for the duration of the reaction. Dry tetrahydrofuran (16 ml) and vinyl chloride (ca. 4 ml) were introduced. The stirred mixture was heated to ca. 40° and two drops of 1,2-dibromoethane was added. The reaction had been initiated when the solvent became light brown. Stirring and periodic heating to 40° were continued until the colour had become dark brown. More vinyl chloride (ca. 10 ml) was condensed into the flask. Dry tetrahydrofuran (120 ml) was added in portions over 2 hr. The presence of vinyl chloride in the mixture was always maintained. Stirring at 30-45° was continued until only traces of magnesium remained. The dry ice--acetone condenser was replaced by a water-cooled condenser. The deep brown solution was heated to 65° and the excess vinyl chloride was vented to the fume hood. To the Grignard solution, cooled and maintained at -10 to -5°, was added dropwise over 2.5 hr a solution of distilled cyclohexanone (27.0 g; 275 mM) in dry tetrahydrofuran (40 ml). After stirring 10 hr at room temperature, the mixture was cooled to 0° and hydrolysed by the slow addition of cold, saturated aqueous ammonium chloride (35 ml). The precipitate was allowed to settle, the clear yellowish solution was decanted, and the solid residue was washed with ether (4 x 100 ml). The combined organic solution was concentrated to an oil, diluted with methylene chloride (200 ml) and dried (anhydr. Na_2SO_4). After removal of solvent, the residue was distilled to give **158** as a colourless liquid (bp 70-71° at 12 torr; lit.[38] bp 65° at 13 torr).

Yield: 29.6 g; 85%.

ir ($CHCl_3$): 3585 cm^{-1} (m); 3420 (bm); 3085 (m); 1637 (m);

1451 (s); 990 (s); 951 (s); 920 (s); 900 (s).

nmr ($CDCl_3$): τ 3.76-4.27 (m, 1H); 4.60-5.15 (m, 2H); 8.36 (s, 1H); 8.46 (bs, 10H).

1-Vinylcyclohexyl Acetate (**153**)

1-Vinylcyclohexanol (**158**; 19.9 g; 0.157 M) was dissolved in cyclohexane (100 ml). An aliquot (10 ml) of this solution was added over 5 min to a stirred, heated (70°) solution of *p*-toluenesulphonic acid monohydrate (100 mg; 0.52 mM) in distilled isopropenyl acetate (180 ml; previously dried over 4A molecular sieve), maintained under nitrogen. After 90% of **158** had reacted (*ca*. 2-3 hr; determined by glpc, UCW-98), a second aliquot (10 ml) of the cyclohexane solution of **158** was added. This procedure was continued until all of **158** had been added. The pale yellow solution was heated for an addition 14 hr and then cooled. Removal of solvents left an oil which was taken up in ether (300 ml), washed with aqueous sodium bicarbonate (5% by wt; 100 ml) and with water (100 ml), concentrated to an oil, diluted with methylene chloride (200 ml), and dried (anhydr. Na_2SO_4). Evaporation of the solvent gave crude **153**. A glpc analysis showed the presence of only trace amounts of **158** (2-3%) and of the diene by-products (2-3%). Distillation of the crude product yielded

153 as a colourless liquid (bp 77° at 7 torr; lit.[139] bp 65° at 1 torr). Unfortunately during the distillation approximately 10% of 154 decomposed to the diene impurities.

Yield: 21.7 g; 82%.

ir ($CHCl_3$): 1725 cm^{-1} (s); 1642 (w); 1370 (s); 1239 (s).

nmr ($CHCl_3$): τ 3.55-4.10 (m, 1H); 4.66-5.07 (m, 2H); 7.99 (s, 3H); 7.57-8.92 (m, 10H).

mass spectrum: calc. for $C_{10}H_{16}O_2$: 168.1150.
meas. *m/e*: 168.1146.

1-Acetoxycyclohexanecarboxaldehyde (159)

A stream of ozonated oxygen (0.33 cu ft/min; 1.95 mM ozone/min) was passed through a sintered glass disc into a stirred, cold (-60°) solution of the allylic acetate 153 (10.0 g; 90% pure; 53.5 mM) in methanol (200 ml). Monitoring the disappearance of 153 by glpc (UCW-98) showed the reaction to be complete after about 1.5 hr (equivalent to 175 mM O_3). After purging ozone from the clear solution (-60°) with dry nitrogen for 1 hr, dimethylsulphide (5.58 g; 90 mM) was then introduced via syringe. The solution was stirred for 1.0 hr at -60°, 1.5 hr at -5°, and 5 hr at room temperature. Removal of solvent left an oil which was poured into water (500 ml) and extracted with

Skelly B (4 x 80 ml). The combined extract was washed with aqueous sodium bicarbonate solution (5% by wt; 50 ml) and with water (50 ml) and was stripped of solvent. The residue was taken up in methylene chloride (50 ml) and dried (anhydr. Na_2SO_4). Concentration of the solution and flash distillation of the residue gave **159** as a colourless liquid (95% pure by glpc; UCW-98).

Yield: 3.36 g; 33%.

ir ($CHCl_3$): 1730 cm^{-1} (s); 1371 (m); 1266 and 1240 (bs).

nmr ($CDCl_3$): τ 0.49 (s, 1H); 7.88 (s, 3H); 7.60-9.00 (m, 10H).

1-(1-Acetoxycyclohexyl)-6-phenylhex-1-en-3-one (**160**)

A solution of the phosphorane **145** (1.51 g; *ca.* 3.5 mM) and **159** (*ca.* 95% pure; 0.500 g; 2.78 mM) in dry toluene (2 ml) under dry nitrogen was heated at 90-100° for two days. The cooled, dark red product was stripped of solvent under reduced pressure, and diluted with cyclohexane. The triphenylphosphonium oxide was removed by filtration. More phosphonium oxide was removed by repeating the above procedure. The crude product was purified by chromatography on silicic acid (30 g; chloroform eluent) and by short-path distillation (0.05 torr; 170-200° bath temperature). The desired compound (**160**) was obtained as a colourless oil. Analysis by tlc (silica gel) showed that a small amount of decomposition had occurred during the distillation.

Yield: 0.620 g; 71%.

ir ($CHCl_3$): 1730 cm^{-1} (s); 1668 (s); 1634 (m); 1234 (s).

nmr ($CDCl_3$): τ 2.80 (bs, 5H); 3.08 (d, J=17Hz, 1H); 3.94 (d, J=17Hz, 1H); 7.17-8.93 (m, 19H).
τ ($C\underline{H}_3COO$) 7.98.

mass spectrum: calc. for $C_{20}H_{26}O_3$: 314.1882.
meas. m/e: 314.1879.

S-Ethyl Heptanethioate (169)

A solution of heptanoic acid (4.01 g; 30.8 mM) and N,N-dimethylformamide (ca. 7 mg; 0.01 mM) in freshly distilled thionyl chloride (3.6 ml; 50.0 mM) was stirred at room temperature for 2 hr, protected from atmospheric moisture by a Drierite drying tube. Excess thionyl chloride was removed under reduced pressure. Remaining traces of thionyl chloride were removed by diluting the residue with dry benzene (15 ml) and then reconcentrating to an oil. This procedure was repeated twice. A solution of the resulting heptanoyl chloride in dry benzene (40 ml) was added over 10 min to a cooled (10°), stirred suspension of lithium ethanethiolate in benzene, previously prepared by adding a hexane solution of n-butyllithium (40.0 ml; 1.52 M; 61 mM) to a cooled (10°), stirred solution of ethanethiol (5.0 g; 81 mM) in dry benzene (100 ml). After stirring overnight at room temperature, the mixture was heated briefly (30 min) at reflux, cooled, poured into dilute aqueous hydrochloric acid (70 ml H_2O and 30 ml 1.0 M aqueous HCl), and extracted with benzene (2 x 50 ml). The combined extract was washed with water (50 ml), concentrated to ca. 6 ml, diluted with methylene chloride (50 ml), dried (anhydr. Na_2SO_4), and stripped of solvent. The resulting oil was filtered through a column of silicic acid (100 g; carbon tetrachloride eluent) and distilled (bp 112° at 23 torr) to give 169 as a colourless oil.

Yield: 4.52 g; 86%.

ir (film): 1694 cm^{-1} (s).

nmr ($CDCl_3$): τ 7.16 (q, J=7Hz, 2H); 7.49 (bt, 2H); 7.9-9.4 (m, 14H).

Heptanal (170): W-1 Raney Nickel Reduction of 169

W-1 Raney nickel was prepared according to the procedure of Covert and Adkins.[140] The Raney nickel was stored under methanol in a tightly sealed bottle.

W-1 Raney nickel (2.0 ml as methanol-moist catalyst; ca. 1.4 g dry wt) was washed three times with acetone (8 ml) to remove the methanol. The catalyst was then refluxed in acetone (8 ml) for 2 hr under nitrogen. After cooling, the acetone was decanted and the catalyst was washed four times with 20% aqueous dioxane (8 ml). A solution of 169 (20.4 mg; 0.117 mM) and cyclododecane (15.0 mg; internal standard for glpc analysis) in 20% aqueous dioxane (11.7 ml) was introduced into the flask containing the moist catalyst. Under nitrogen, the mixture was heated at 60° and the progress of the reaction was followed by glpc (UCW-98). By referring to the glpc traces of standard solutions of heptanal and cyclododecane and of 169 and cyclododecane, the amounts of heptanal and the thiol ester were calculated. The results are summarized in Table 14.

trans-3-Decen-2-one (172)

A solution of heptanal (0.268 g; 1.99 mM) and acetylmethylenetriphenylphosphorane[94] (171; 0.734 g; 2.30 mM) in benzene (5 ml) was refluxed for 15 hr, cooled, concentrated to ca. 1.0 ml under reduced pressure, and diluted with pentane (6 ml). After filtration to remove the precipitate, the filtrate was again concentrated, diluted with pentane and filtered. Final removal of solvent and flash distillation afforded pure 172.

Yield: 0.300 g; 92%.

ir ($CHCl_3$): 1690 cm^{-1} (shoulder); 1670 (s); 1637 (shoulder); 1625 (s); 980 (s).

nmr ($CDCl_3$): τ 3.17 (dt, J_d=16 Hz, J_t=6.5 Hz, 1H); 3.95 (dt, J_d=16 Hz, J_t=1.2 Hz, 1H); 7.53-8.01 (m, 5H); 8.70-9.35 (m, 11H).

Table 14: Reduction of S-Ethyl Heptanethioate with Raney Nickel

Reaction Time (hr)	Thiol Ester mg (%)	Heptanal mg (%)
0	20.4 (100)	0 (0)
.25	9.0 (44)	5.5 (41)
1.25	3.8 (19)	7.8 (58)
5.7	trace	10 (75)

trans-3-Decen-2-one (172) from 169 and 171

W-1 Raney nickel (4.0 ml as moist catalyst; *ca.*

2.8 g dry wt) was partially deactivated and washed with aqueous dioxane as described previously on page 220. To the washed catalyst was added a solution of S-ethyl heptanethioate (**169**; 50.1 mg; 0.288 mM), acetylmethylenetriphenylphosphorane (**171**; 92.0 mg; 2.89 mM), and cyclododecane (28.7 mg; internal glpc standard) in 20% aqueous dioxane (7 ml). The mixture was stirred under nitrogen for 4.25 hr at 60°, cooled, and filtered. The filtrate was then heated at reflux for 11 hr. Glpc analysis (UCW-98) of the reaction mixture and of a standard solution of **172** and cyclododecane indicated a yield of 52% for **172**. Although heptanal was still present in the crude product, extended heating at reflux did not improve the yield.

Ethyl Hydrogen Adipate (**173**)

The procedure reported for the preparation of ethyl hydrogen sebacate was used with little modification.[141]

A mixture of adipic acid (201 g; 1.38 mole), diethyl adipate (100 g, 0.472 mole), absolute ethanol (36 ml; 0.62 mole) and concentrated aqueous hydrochloric acid (28 ml) in dry di-*n*-butylether (distilled from calcium hydride; 75 ml) was heated at reflux until the mixture became homogeneous. The temperature of the pot was lowered to 125°, absolute ethanol (43 ml, 2.0 mole) was added, and the solution was refluxed 11 hr. Additional absolute ethanol (20 ml, 0.82 mole) was added. After 5 hr reflux, the solution was cooled to 75° and the solvents were removed under reduced pressure (20 torr). The pot temperature was slowly raised to 125° at 20 torr. When no further solvent distilled, the residue was cooled, tested as neutral to moist pH paper, and fractionally distilled using a spinning-band column. The crude ethyl hydrogen adipate (bp 105-110° at 6 torr) was redistilled to afford pure **173** as a colourless oil. (bp 105-108° at 6 torr; lit.[142a] bp 155-6° at 7 torr).

Yield: 123 g; 44% (based on adipic acid).

ir ($CHCl_3$): 3630-2410 cm^{-1} (bm); 1713 (s).

nmr ($CDCl_3$): τ -1.26 (s, 1H); 5.86 (q, J=7.5 Hz, 2H); 7.35-7.90 (m, 4H); 7.90-8.50 (m, 4H); 8.76 (t, J=7.5 Hz, 3H).

5-Ethoxycarbonylpentanoyl Chloride (**174**)

Ethyl hydrogen adipate (110 g; 0.633 mole) and distilled thionyl chloride (150 g; 1.26 mole) were mixed in a flask protected from atmospheric moisture by a Drierite drying tube. N,N-Dimethylformamide (50 mg; 0.68 mM) was then added and the solution was stirred for 8 hr at room temperature. The solution was warmed to *ca*. 40° and the excess thionyl chloride was stripped from the product at slightly reduced pressure. The remaining trace of thionyl chloride was removed by coevaporation with dry benzene. The dark oil was distilled (bp 115° at 10 torr; lit.[142a] bp 114-115° at 1 torr) to give pure 174.

Yield: 119 g; 98%.

ir (film): 1804 cm^{-1} (s); 1731 (s); 1180 (bs).

nmr (CCl_4): τ 5.92 (q, J=5 Hz, 2H); 7.06 (m, 2H); 7.72 (m, 2H); 8.0-8.5 (m, 4H); 8.77 (t, J=7.5 Hz, 3H).

Undecanedioyl Chloride (176)

Distilled oxalyl chloride (60 g; 0.47 mole) was added to a mixture of undecanedioic acid (25.0 g; 0.115 mole; prepared from 174 as described in reference 142) in dry benzene (30 ml) at 0°. The reaction was warmed to room temperature and stirred overnight, protected from moisture by a Drierite drying tube. Benzene and excess oxalyl chloride were stripped off at room temperature under reduced pressure (20 torr). The remaining trace of oxalyl chloride was removed by coevaporation with dry benzene. Undecanedioyl chloride was obtained as a yellow oil.

S-Ethyl 10-Carboxydecanethioate (177)

The reaction of an acid chloride with ethanethiol has been previously reported to proceed in high yield.[143]

An aliquot (15 ml) of a solution of ethanethiol (9.50 ml; 7.90 g; 0.127 mole) in dry benzene (100 ml) was added dropwise into stirred undecanedioyl chloride (prepared from 0.115 mole 175) under nitrogen at 30-35°. The solution was stirred at this temperature for 3-4 hr. A second aliquot (15 ml) of the ethanethiol solution was added dropwise and again the solution was stirred for 3-4 hr. This procedure was continued until all of the ethanethiol had been added. After additional stirring at 30-35° for 12 hr, the solution was heated to 100° to remove the excess ethanethiol and much of the benzene. After cooling, remaining acid chloride was hydrolysed by the slow addition of aqueous potassium hydroxide solution (7% by wt) until the pH tested between 6-7. After 3 hr stirring, the pH of the mixture was readjusted to 6-7 with more aqueous base. Two hours stirring produced little change in the acidity of the mixture. The pH of the mixture was then adjusted to *ca*. 1.5 with diluted aqueous hydrochloric acid (3% by wt), during which an off-white precipitate formed. The mixture was extracted with methylene chloride (4 x 100 ml) and the combined extract was washed with water (100 ml), dried (anhydr. Na_2SO_4), and concentrated to a yellow-orange solid. The solid was dissolved in the minimum volume of dry tetrahydrofuran and diluted with pentane (300 ml). The precipitate (mainly undecanedioic acid) was removed by filtration and was washed with a little benzene. The benzene washing and filtrate were combined and concentrated to an oil. Silica gel chromatography (430 g; 5% ethyl acetate--benzene eluent) gave 177 as a pale yellow solid (mp 48.7-49.5°, recrystallized from ether--pentane).

Yield: 9.66 g; 32%.

ir ($CHCl_3$): 3502 cm^{-1} (w); 3500-2700 (bm); 1704 (s); 1678 (s).

nmr ($CDCl_3$): τ-0.08 (bs, 1H); 7.12 (q, J=7 Hz, 2H); 7.32-7.88 (m, 4H); 7.88-8.95 (m, 17H). τ ($C\underline{H}_3CH_2SCO$) 8.77 (t, J=7 Hz).

analysis: Calcd. for $C_{13}H_{24}O_3S$: C, 59.96; H, 9.29; S, 12.31.

Found: C, 59.68; H, 9.24; S, 12.11.

mass spectrum: calcd. for $C_{13}H_{24}O_3S$: 260.1447.

meas. *m/e*: 260.1442.

S-Ethyl Chlorocarbonyldecanethioate (178)

A solution of 177 (1.12 g; 4.31 mM) and freshly distilled oxalyl chloride (2.5 ml; 3.7 g; 29 mM) in benzene (2.0 ml), protected from atmospheric moisture by a Drierite drying tube, was stirred at room temperature for 6 hr. Benzene and excess oxalyl chloride were removed at room temperature under reduced pressure. The remaining trace of oxalyl chloride was removed by coevaporation with dry benzene. Compound **178** was obtained as a yellow oil.

ir (CCl_4): 1800 cm^{-1} (s), 1735 (w); 1693 (s).

nmr (CCl_4): τ 6.90-7.33 (m, 4H), 7.33-7.83 (m, 2H); 8.00 9.00 (m, 17H). τ ($CH_3C\underline{H}_2S$-) 7.13 (q, J=7 Hz). τ ($C\underline{H}_3CH_2S$-) 8.75 (t, J=7 Hz).

S-Ethyl 12-Bromo-11-oxoundecanethioate (**180**)

To a stirred, cold (-10°) ethereal solution of diazomethane (27 ml; 0.49 M, 13 mM) under nitrogen was added over 15 min a solution of **178** (prepared from 4.3 mM **177**) in dry ether (15 ml). After stirring 6 hr between -5 and 0°, the yellow solution was evaporated at room temperature to a yellow oil. The crude diazoketone **179** was diluted with dry tetrahydrofuran (10 ml) and reconcentrated.

Aqueous hydrobromic acid solution (48.2%; 0.75 g; 4.5 mM HBr) was added, over 3 min, to a cold (-20°), stirred solution of **179** in dry tetrahydrofuran (10 ml). After addition was completed, the yellow solution was stirred for 15 min at 0°, poured into water (50 ml), and extracted with methylene chloride (4 x 40 ml). The combined extract was washed with water (2 x 40 ml), concentrated to *ca*. 2 ml, diluted with methylene chloride, dried (anhydr. Na_2SO_4), and reconcentrated at room temperature to a light brown solid. Removal of minor impurities by silicic acid chromatography (28 g; chloroform eluent) afforded 180 as a pale yellow solid.

Yield: 1.31 g; 90% from 177.

ir (CH_2Cl_2): 1720 cm^{-1} (s), 1683 (s).

nmr (CCl_4): τ 6.22 (s, 2H); 6.94-7.72 (m, 6H); 8.10-8.96 (m, 17H).

11-Ethylthiocarbonyl-2-oxoundecyltriphenylphosphonium Bromide (182)

A solution of triphenylphosphine (1.02 g; 3.89 mM) in dry benzene (5 ml) and dry heptane (4.5 ml) was added with stirring at room temperature to a solution of 180 (1.196 g; 3.55 mM) in dry benzene (5 ml) and dry heptane (4.5 mol) under nitrogen. The pale yellow solution deepened in colour and after 15 min a small amount of orange oil separated from the turbid solution. After 45 min heating at 65°, approximately 1-2 g of oil had separated from solution. The mixture was stirred and heated an additional 1.25 hr at 65° and then cooled. The solvents were removed at 35° by rotary evaporation and the resulting oil was chromatographed on silicic acid (93 g). Unreacted triphenylphosphine, 180, and the by-product 183 were eluted readily with chloroform. The desired phosphonium bromide (182) was eluted with 1% methanol--chloroform as a yellow-orange oil.

Yield: *ca*. 1.58 g; 74%.

ir ($CHCl_3$): 3310 cm^{-1} (w); 1710 (s); 1679 (s); 1437 (s); 1104 (s).

nmr ($CDCl_3$): τ 1.95-2.80 (m, 15H); 4.15 (d, J=11.5 Hz, 2H); 6.88-7.70 (m, 6H); 8.10-9.27 (m, 17H). τ ($CH_3\underline{CH_2}S$-) 7.18 (q, J=7 Hz).

11-Ethylthiocarbonyl-2-oxoundecylidenetriphenylphosphorane (168)

A methylene chloride solution of phosphonium bromide 182 (0.802 g; 1.34 mM) was dried 15 hr over 4A molecular sieve. The solvent was replaced by dry benzene (20 ml). The cooled (5°) solution was treated with a hexane solution of *n*-butyllithium (1.54 *M*; 0.845 ml, 1.30 mM). The smell of mercaptan was detected during the reaction. (*n*-Butyllithium was a poor choice of base. For comment see page 102.) After stirring for 15 min, the solution, which contained a fine precipitate, was poured into water (60 ml) and shaken. The mixture was extracted with benzene (3 x 40 ml) and the combined extract was concentrated to a heavy oil, diluted with methylene chloride (30 ml), and dried (anhydr. Na_2SO_4). Removal of solvent gave crude 168 as a pale yellow oil.

Yield: ca. 0.605 g; 87%.

ir (CCl_4): 1687 cm^{-1} (s), 1530 (s); 1434 (s); 1110 (s).

nmr ($CDCl_3$): τ 2.0-2.83 (m, 15H); 5.9-6.7 (ill-defined, 1H); 7.15 (q, J=7.2 Hz, 2H); 7.35-7.97 (m, 4H); 7.97-8.98 (m, 17H); 8.98-9.22 (m, impurity).

Raney Nickel Reduction of 168

The activity of a batch of W-1 Raney nickel was standardized using S-ethyl heptanethioate as a test substrate. The methanol-moist W-1 Raney nickel (28 ml; ca. 19.5 g dry wt) was washed thoroughly with freshly distilled, purified acetone (3 x 40 ml) to remove the methanol. The catalyst, in purified acetone (50 ml), was stirred at reflux under nitrogen for 2 hr. After cooling, the acetone was decanted and the catalyst was thoroughly washed with 20% aqueous dioxane (5 x 40 ml). To the catalyst was then added a solution of crude 168 (ca. 80% pure;

0.55 g; 0.85 mM; .0067 *M*) and cyclododecane (18.7 mg; internal glpc standard) in 20% aqueous dioxane (150 ml). The mixture was stirred at 60° under nitrogen for 5 hr, cooled, and filtered. The catalyst was washed with dioxane (2 x 25 ml). The combined washings and filtrate was diluted with heptane (50 ml) and washed with saturated aqueous sodium chloride solution (2 x 100 ml). The combined aqueous washings was back-extracted with heptane (2 x 50 ml). All organic solutions were combined (*ca.* 360 ml; 0.0024 *M* in phosphorane), dried briefly (anhydr. Na_2SO_4), and heated at reflux (90-95°) under nitrogen. The progress of the reaction was monitored by glpc (UCW-98). There appeared to be no further reaction after 52 hr. After 7 days, the solution was concentrated to *ca.* 4 ml by careful spinning-band distillation. The residue was diluted with pentane, cooled to -15°, filtered to remove triphenylphosphonium oxide, and stripped of solvent. The procedure was repeated twice. From the clear concentrate (*ca.* 2 ml) a small amount of yellow oil separated to the bottom of the flask. The oil showed no peaks on glpc (UCW-98). On the other hand, glpc analysis (UCW-98) of the solution indicated the presence of cyclododecane as well as five main products (yields roughly 3-5% based on **168**) with retentions equal to or longer than that of cyclododecane. Analysis of the mixture by glpc-mass spectrometry showed the product with the second shortest retention time (retention time: +4.0 min relative to cyclododecane; 6 ft UCW-98; temperature programmed from 90° to 200° at 10 /min) to have an apparent molecular ion at *m/e* 180.

S-Ethyl 11-Hydroxyundecanethioate (**187**)

A solution of borane in tetrahydrofuran (1.0 *M*; 14.5 ml; 14.5 mM) was introduced, over 30 min, into a stirred, cold (-18°) solution of **177** (3.20 g; 12.3 mM) in dry tetrahydrofuran (20 ml), maintained under nitrogen. The solution was then stirred overnight at -18°, hydrolysed with aqueous hydrochloric acid (7.5% by wt; 5 ml; 12 mM), and saturated with sodium chloride. The upper organic layer was decanted and the aqueous layer was extracted with ether (3 x 6 ml). All organic solutions were combined, stripped of solvent, diluted with methylene chloride (30 ml), dried (anhydr. Na_2SO_4), and reconcentrated to an oil. Chromatography of the oil on silica gel (62 g; 3% ethyl acetate--benzene eluent) afforded pure **187** (mp 29.0-29.8°; recrystallized from ether--pentane).

Yield: 2.21 g; 73%.

ir (CCl_4): 3620 cm^{-1} (m); 3600-3100 (m); 1691 (s).

nmr ($CDCl_3$): τ 6.41 (bt, 2H); 7.03 (s, 1H); 7.14 (q, J=

7.5 Hz, 2H); 7.47 (bt, 2H); 8.07-9.00 (m, 19H).

mass spectrum: calcd. for $C_{13}H_{26}O_2{}^{32}S$: 246.1654.

meas. m/e: 246.1658.

analysis: calcd. for $C_{13}H_{26}O_2S$: C, 63.37; H, 10.64; S, 13.01.

found: C, 63.11; H, 10.82; S, 12.85.

11-Hydroxyundecanoic Acid (188)

A solution of hydroxy thiol ester 187 (1.017 g; 4.13 mM) in 20% aqueous ethanol (3 ml) was treated with a solution (0.924 M; 4.93 ml; 4.55 mM) of potassium hydroxide in 20% aqueous ethanol. After heating for 1.5 hr at 75°, the solution was cooled, neutralized to pH 6 with aqueous hydrochloric acid (10% by wt) and stripped of solvent at 30°. The resulting white solid was mixed with water (30 ml) and the pH of the mixture was adjusted to 1.0 with concentrated aqueous hydrochloric acid. After one extraction with ether (20 ml), the aqueous layer (pH 1-2) was saturated with sodium chloride and further extracted with ether (4 x 20 ml). The combined extract was concentrated to a solid, diluted with methylene chloride (50 ml), and dried (anhydr. Na_2SO_4). Removal of solvent afforded 188 as a white solid (mp 67.7-68.5°; recrystallized from water; lit.[144] mp 68-69°).

Yield: 0.850 g; 100%.

ir ($CHCl_3$): 3600-2400 cm^{-1} (m); 1709 (s); 1229 (bs).

nmr ($CDCl_3$): τ 2.81 (bs, 2H); 6.36 (bt, 2H); 7.67 (bt, 2H); 8.14-9.05 (m, 16H).

11-Acetoxyundecanoic Acid (189)

A solution of 11-hydroxyundecanoic acid (188) (0.830 g; 4.10 mM) and acetic anhydride (0.410 g; 40.6 mM) in dry pyridine (10 ml) was heated under nitrogen at 70° for 6 hours, cooled, stripped of pyridine and acetic anhydride (30°, 0.01 torr), diluted with dry xylene (10 ml), and reconcentrated to an oil. The oil (mainly the acetoxy anhydride) was stirred in aqueous tetrahydrofuran (1:1 by vol; 15 ml) at 75° for 1.5 hr. The pH of the cooled mixture was adjusted to 1.0 with concentrated aqueous hydrochloric acid. The mixture was saturated with sodium chloride and extracted with ether (5 x 7 ml). The combined extract was concentrated to *ca*. 2 ml, diluted with methylene chloride (20 ml), washed to pH 3-4 with sodium chloride solution (50% saturated), and dried (anhydr. Na_2SO_4). Removal of solvent and chromatography on silicic acid (14 g; 30-50% chloroform--carbon tetrachloride eluent) gave 189.

Yield: 0.828 g; 83%.

ir ($CHCl_3$): 3600-2400 cm^{-1} (m); 1720 (2 peaks, s); 1365 (m); 1237 (bs).

nmr ($CDCl_3$): τ -1.37 (s, 1H); 5.93 (bt, 2H); 7.65 (bt, 2H); 7.94 (s, 3H); 8.04-8.92 (16H).

11-Acetoxyundecanoyl Chloride (190)

A solution of 11-acetoxyundecanoic acid (189; 0.767 g; 3.14 mM) and freshly distilled oxalyl chloride (3 ml; 4.5 g; 35 mM) in dry benzene (3 ml) was stirred at room temperature for 4 hr. Under reduced pressure and at room temperature, the solution was concentrated to ca. 0.6-1.0 ml. The remaining trace of oxalyl chloride was removed by coevaporation with dry benzene (3 x 5 ml). The residue was a pale yellow oil.

12-Acetoxy-1-bromo-2-dodecanone (192)

To a stirred ethereal solution of diazomethane (0.42 M; 22.5 ml; 9.45 mM) at 0° under nitrogen was added, slowly over 10 min, a solution of 190 (3.14 mM 189) in dry ether (10 ml). After stirring 5 hr at 0°, the mixture was allowed to stir 4 hr at room temperature. The yellow solution was stripped of solvent and excess diazomethane. The yellow residue was diluted with dry tetrahydrofuran

(15 ml) and again concentrated to give crude diazoketone **191**.

The diazoketone in dry tetrahydrofuran (10 ml) at -20° under nitrogen was decomposed rather slowly by slowly adding over 3 min aqueous hydrobromic acid (48%; 0.53 g; 3.44 mM). The solution was then stirred 20 min at 0°, 20 min at room temperature, poured into water (30 ml), saturated with sodium chloride, and extracted with methylene chloride (4 x 15 ml). The combined extract was washed with water and dried (anhydr. Na_2SO_4). Removal of solvent and chromatography of the yellow oil on silicic acid (40 g; chloroform--carbon tetrachloride eluent) gave **191** as a white solid (mp 38.5-39.5°; recrystallized from pentane).

Yield: 0.751 g; 75% from **189**.

ir (CCl_4): 1740 cm^{-1} (s); 1720 (s); 1368 (m); 1240 (s).

nmr ($CDCl_3$): τ 6.02 (bt, 2H); 6.24 (s, 2H); 7.38 (bt, 2H);
8.02 (s, 3H); 8.18-8.91 (m, 16H).
τ ($ClC\underline{H}_2CO$; 10%) 6.07 (s).

1-Bromo-12-hydroxy-2-dodecanone (**193**)

A stirred solution of **192** (0.338 g; 1.05 mM) and *p*-toluenesulphonic acid monohydrate (10 mg; 0.052 mM) in dry methanol (10 ml) was refluxed under nitrogen for 11 hr. Removal of solvent and chromatography of the solid residue on silicic acid (11 g; chloroform eluent) afforded 193 as a white solid (mp 77.0-77.2°; recrystallized from carbon tetrachloride).

Yield: 0.255 g; 87%.

ir ($CHCl_3$): 3612 cm^{-1} (m); 3600-3100 (m); 1715 (s).

nmr ($CDCl_3$): τ 6.12 (s, 2H); 6.36 (bt, 2H); 7.34 (bt, 2H); 8.20-9.10 (m, 17H). τ ($ClC\underline{H}_2CO$, 10%) 5.94 (s). τ ($CH_2O\underline{H}$) 3.32 (s).

mass spectrum: calcd. for $C_{12}H_{23}{}^{79}BrO_2$: 278.0881.
meas. m/e: 278.0882.

12-Bromo-11-oxododecanal (194)

Chromium trioxide--pyridine complex was prepared by the method of Dauben and coworkers.[145]

Methylene chloride (10 ml, dried over 4A molecular sieve) was treated with chromium trioxide--pyridine complex (20 mg; 0.078 mM) under nitrogen, stirred 20 min, and centrifuged. The clear centrifugate was decanted onto chromium trioxide--pyridine complex (351 mg; 1.36 mM). After stirring the deep burgundy solution for 15 min at room temperature, a solution of the bromo alcohol 193 (recrystallized from carbon tetrachloride; mp 77.0-77.2°; 62.3 mg; 0.223 mM) in dry methylene chloride (1.5 ml) was quickly added. The solution immediately turned brown-black. After stirring 1.5 min at room temperature, ethanol (ca. 0.7 ml) was added and the mixture was stirred for an additional 30 sec. The solution was decanted into cold (0°), stirred ether (20 ml) and the black tar remaining in the flask was washed with ether (3 x 5 ml). The combined ether solutions was filtered to remove the brown precipitate. The light brown filtrate was quickly washed with dilute aqueous hydrochloric acid (1.0 M; 2 x 8 ml) and with aqueous sodium chloride solution (50% saturated; 2 x 5 ml). The solvents were evaporated and the residue was dissolved in methylene chloride (10 ml) and dried (anhydr. Na_2SO_4). Removal of solvent and filtration of the resulting light-brown solid on silca gel (1.0 g; 5% ethyl acetate--benzene eluent) afforded pure 194 as a white solid.

Yield: 57.4 mg; 93%.

ir (CCl_4): 2710 cm^{-1} (m); 1727 (s).

nmr (CCl_4): τ 0.38 (t, J=1.5 Hz, 1H); 6.20 (s, 2H); 7.21-7.90 (m, 4H); 8.10-8.96 (m, 14H). τ ($ClC\underline{H}_2CO$; 10%) 6.03 (s).

11-Formyl-2-oxoundecyltriphenylphosphonium Bromide (184)

To 12-bromo-11-oxodecanal (183; ca. 50 mg; 0.18 mM) dissolved in dry benzene (1.0 ml) and dry heptane

(0.6 ml), was added a solution of triphenylphosphine (57.8 mg; 0.220 mM) in dry benzene (0.6 ml) and dry heptane (0.5 ml). During the reaction a heavy colourless oil settled out of the solution. The solution, maintained under nitrogen, was stirred at 62° for 2.5 hr, cooled, concentrated at room temperature to a viscous oil, and pumped out (2 days; 0.01 torr). The crude phosphonium bromide remained as a colourless oil. As expected, the nmr spectrum showed the presence of some benzene and heptane.

nmr ($CDCl_3$): τ 0.27 (t, J=1.6 Hz, 1H); 1.80-2.70 (m, >15H); 4.04 (d, J=11.5 Hz, 2H); 7.01 (m, 2H); 7.58 (m, 2H); 8.10-9.10 (m, >14).

Cyclododecenones and Cyclododecanone from Phosphonium Salt 184

a) Experiment 1

A solution of the phosphonium salt 184 (prepared from *ca.* 11 mg of bromo aldehyde 194; 0.040 mM) in dry methanol (2 ml) was diluted with dry toluene (20 ml), cooled under nitrogen to -78°, and treated with methanolic sodium methoxide solution (0.0100 *M*; 3.17 ml; 0.0317 mM). After slowly warming to room temperature, the solution was further diluted with dry toluene (18 ml). The solution was slowly distilled through a spinning-band column until

18 ml of distillate had been collected. (The purpose of the distillation was to remove the small amount of methanol present.) The remaining solution (25 ml; ca. 1-3 x 10^{-3} M in "phosphorane") was heated at reflux under nitrogen for 100 hr. Following concentration to 3 ml by careful spinning-band distillation (1 atmosphere), the reaction solution was diluted with pentane, cooled to 0°, filtered, and reconcentrated. Glpc-mass spectral analysis (Carbowax 20m) of the crude product showed the presence of three cyclododecenones A, B, and C, each exhibiting a molecular ion at m/e 180. Benzyl alcohol, benzaldehyde, and 1,2-diphenylethane contaminated the cyclization products. These by-products were identified from their mass spectra.

For a quantitative analysis of the three cyclododecenones, tetradecane (0.307 mg) was added to the concentrate. Authentic trans-2-cyclododecenone was synthesized by the method of Nozaki and coworkers.[98] The cyclododecenone isomer C and trans-2-cyclododecenone exhibited identical mass spectra and identical retention times on glpc (Carbowax 20m, UCW-98, Reoplex). The results are summarized in Table 2.

b) Experiment 2

The procedure employed was largely the same as that described for Experiment 1. After removal of the methanol by spinning-band distillation, the toluene solution (2.9×10^{-4} M) contained approximately 0.011 mM of "phosphorane". The solution was then degassed (3x), sealed in a 100-ml Carius tube, and heated at 200° for 100 hr. Work-up and product analysis were by the same methods as outlined for Experiment 1. The results are summarized in Table 2.

c) Experiments ($1,H_2$) and ($2,H_2$)

Each reaction concentrate, containing tetradecane, was hydrogenated (1 atm H_2) in ethyl acetate (4-5 ml) over 5% palladium on charcoal (20-25 mg). After 24 hr, each mixture was filtered and the catalyst was washed with ether (4 x 1 ml). The combined filtrate and washings was concentrated to 2 ml by spinning-band distillation. Glpc analysis indicated that the cyclododecenone isomers A, B, and C were not present. In their place was cyclododecanone (identical to authentic cyclododecanone based on mass spectrometry and glpc). The overall yields of cyclodecanone from the cyclization (Experiments 1 and 2) and the hydrogenation [Experiments ($1,H_2$) and ($2,H_2$)] steps are summarized in Table 2.

4,6-Cycloheptadiene-1,3-dicarboxylic Acid (210)

Sodium amalgam (3%) was prepared according to the procedure in reference 101b.

3,5,7-Cycloheptatriene-1,3-dicarboxylic acid (201; 10.53 g; 58.6 mM), prepared by the method of Vogel and coworkers,[99b] was dissolved in aqueous sodium hydroxide solution (0.970 M; 121 ml; 117 mM). Into the homogeneous solution was mixed an aqueous sodium acetate solution (15.5 g sodium acetate; 35 ml H_2O). Sodium amalgam (3% Na by wt; small pieces; 220 g; 288 mM) was slowly introduced, in small portions (10 g; 13 mM) over ca. 2 hr, into the vigorously stirred, cold (0-5°) solution of the dicarboxylate salt. Immediately after the addition of each 10 g portion sufficient aqueous acetic acid (50% by vol) was added to maintain the pH of the mixture at 8. [During the initial stages of the reaction, the theoretical amount (ca. 1.5 ml) of aqueous acetic acid was required. The pH of the solution could not be held constant at 8.0 but rather it varied between 7.5 and 9. As the reaction proceeded though, gradually less acetic acid was necessary and the pH could be more easily maintained near 8.] An additional quantity of amalgam (60 g; 78 mM) was added all at one time. The mixture was stirred 1.0 hr during which the pH was controlled at 8 by the occasional addition of one or two drops of aqueous acetic acid. The liquid was then decanted, washed with pentane (2 x 60 ml), and acidified to pH 1.0 with cold aqueous sulphuric acid (20% by wt; ca. 85 ml). After standing for several hours, the white precipitate (210) was collected by filtration and washed with cold (5°) water until the washings tested at pH 3. The filtrate and washings were combined, saturated with sodium chloride, and extracted with ether (6 x 80 ml). The combined ethereal extract was washed with cold (5°) water (3 x 60 ml), dried (anhydr. $MgSO_4$), and stripped of solvent to give more 210 as a white solid. The two lots of 210 were combined. The product was pulverized and dried under reduced pressure (0.01 torr; 40°).

Yield: 10.44 g; 98%.

ir (KBr): 3600-2000 cm^{-1} (bs); 1680 (bs); 1232 (bs); 1250 (bs).

nmr: The sample was prepared by suspending 210 in D_2O (0.5 ml) and adding the minimum amount of a D_2O solution of NaOD to effect complete dissolution of the dicarboxylic acid. The pH of the solution was 6. An external standard of tetramethylsilane was used. τ 4.00-4.40 (m, 4H); 6.50-6.95 (m, 2H); 7.44-8.33 (m, 2H).

4,6-Cycloheptadiene-1,3-dicarboxylic Anhydride (**215**)

A mixture of *cis*-, and *trans*-4,6-cycloheptadiene-1,3-dicarboxylic acid (**210**; 4.40 g; 24.7 mM) was added in one portion to a stirred, hot (100-105°) mixture of acetic anhydride (20 ml) and pyridine (2 ml). After stirring for 20 min at 100-105°, the solution was cooled and the solvents were removed at room temperature under reduced pressure (*ca*. 0.02 torr). The brown solid residue was pulverized to a coarse powder. Dry xylene (15 ml) was added and after brief stirring was removed at 30° under reduced pressure. To ensure complete removal of acetic anhydride and pyridine, trituration with xylene and evaporation were repeated. The powder was then washed with pentane (3 x 10 ml) and sublimed (60-65° at 0.02 torr) on to a cold finger (-10°) to give **215** as a white crystalline solid (mp 84.8-86.0°; recrystallized from ether).

Yield: 3.24 g; 80%.

ir ($CHCl_3$): 1807 cm^{-1} (s), 1759 (s); 1603 (m); 1023 (s).

nmr ($CDCl_3$): τ 3.80 (bs, 4H); 6.07 (m, 2H); 3.57 (m, 1H); 2.23 (m, 1H).

cis-4,6-Cycloheptadiene-1,3-dicarboxylic Acid (**214**)

A solution of the anhydride **215** (0.330 g; 2.01 mM) in purified tetrahydrofuran (5.0 ml) and water (1.0

ml) was heated for 8 hr at 65°, cooled, and concentrated at 30° under reduced pressure to a white solid which was dried for 3 days at reduced pressure (0.01 torr at room temperature). mp 285-290° (decomposition); recrystallized from ether--hexane.

Yield: 0.366 g; 100%.

analysis: calcd. for $C_9H_{10}O_4$: C, 59.33; H, 5.54.

found: C, 59.39; H, 5.62.

Dimethyl *cis*-4,6-Cycloheptadiene-1,3-dicarboxylate (213)

To the dicarboxylic acid 214 (0.100 g; 0.550 mM), suspended in cold (5°) ether (2 ml), was added (dropwise) methanol until all 214 had dissolved. After rapid treatment with an excess of ethereal diazomethane, the solution was stripped of solvents and of excess diazomethane. The oil was diluted in methylene chloride (2 ml) and dried (anhydr. Na_2SO_4). Removal of solvent afforded 213 as a colourless oil.

Yield: 0.116 g; 100%.

ir ($CHCl_3$): 1740 cm^{-1} (s); 1437 (m).

nmr (100.1 MH_3, $CDCl_3$): τ 3.80-4.36 (m, 4H); 6.28 (s, 6H); 6.50 (cd, J=*ca*.10 Hz, 2H); 7.47 (cdt, J_d=13.5Hz, J_t≈3.6 Hz, 1H); 7.82 (dt, J_d=13.5 Hz, J_t≈11.0 Hz, 1H).

Dimethyl 4,5-Epoxy-6-cycloheptene-1,3-dicarboxylate (227 and 228)

A solution of 214 (2.00 g; 11.0 mM) in methylene chloride (100 ml) and dry tetrahydrofuran (20 ml) was treated at room temperature under nitrogen with *m*-chloroperbenzoic acid (85.0%; 2.63 g; 12.9 mM). After stirring for 24 hr, the solution was cooled to 0° and esterified using an excess of dry ethereal diazomethane. The solvents were removed (20°; 20 torr) and the residue was diluted with methylene chloride (30 ml) and dried (anhydr. Na_2SO_4). Removal of solvent then afforded a mixture of 227, 228, and methyl *m*-chlorobenzoate as a colourless oil.

nmr (100.1 MHz, CCl_4): τ 2.10-2.90 (m); 3.95-4.55 (m, *ca.* 2H); 6.19 (s); 6.32-6.44 (4s; 6H); 6.44-7.25 (m, 4H); 7.50-8.31 (m, 2H). τ ($C\underline{H}_3O_2C$, epoxide A) 6.35 (s) and 6.41 (s). τ ($C\underline{H}_3CO_2$, epoxide B) 6.36 (s) and 6.42 (s). τ ($C\underline{H}_3CO_2$, 213) 6.41 (s).

Methyl 4-Methyl-7-oxo-6-oxabicyclo[3.2.2]non-2-ene-9-carboxylate (233)

This experiment was performed by Dr. H. Yamamoto. In preparation for the reaction, all traces of water were removed from the monoepoxides **227** and **228** by coevaporation with dry xylene under reduced pressure at 30°.

To a stirred suspension of dried (80° at 20 torr for 15 hr) cuprous iodide (4.18 g; 22.0 mM) in dry ether (200 ml) at -30° under nitrogen was added a hexane solution of methyllithium (1.66 *M*; 26.5 ml; 44 mM) over 10 min. During the addition the ether mixture first developed a yellow colour, which disappeared in the end to afford a pale grey (or tan) solution. The solution of lithium dimethylcuprate was stirred at -30° for an additional 30 min. Then a solution of the crude monoepoxides **227** and **228** (prepared from 11.0 mM of **214**) in dry ether (30 ml) was introduced over *ca*. 5 min. The resulting yellow suspension was stirred at -20° for 1.25 hr before quenching with saturated aqueous ammonium chloride solution (125 ml). The reaction mixture was stirred for 10 min at 10-20°, the ether layer was decanted and the aqueous layer was extracted with ether (4 x 75 ml). (The colourless aqueous layer rapidly became deep blue when exposed to air.) The combined ethereal solution was washed with saturated aqueous sodium chloride solution (2 x 50 ml), stripped of solvent, diluted with methylene chloride (30 ml), and dried (anhydr. Na_2SO_4). Evaporation of the solvent, followed by chromatography of the yellow residue on silicic acid (125 g; 14% ether in benzene eluent), afforded the desired lactone (ca. 0.80 g; 37%) as a white solid. Pure 233 was obtained by recrystallization from cyclohexene (mp 64-65°).

Yield: 0.615 g; 27%.

ir ($CHCl_3$): 1741 cm^{-1} (s).

nmr (100.1 MHz, $CDCl_3$): τ 4.19 (ddd, J=10.5, 8.5, 2.2 Hz, 1H); 4.48 (ddt, J_d=10.5, 0.9 Hz, J_t=1.5 Hz, 1H); 5.22 (cdd, J=3.7, 1.0 Hz, 1H); 6.25 (s, 3H); 6.73-7.20 (m, 3H); 7.51 (m, 2H); 8.87 (d, J=7.3, 3H).

analysis: calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71.
found: C, 62.83; H, 6.80.

1,4-Cyclohexanecarbolactone (244)

This compound was prepared by Dr. G. O. Spessard according to reported methods. Thus catalytic hydrogenation (35-57 psi H_2; 95% ethanol; 5% rodium on alumina) of ethyl p-hydroxybenzoate,[112a] followed by saponification, afforded a mixture of cis- and trans-4-hydroxy-1-cyclohexanecarboxylic acid. Lactonization under the influence of hot acetic anhydride and pyridine and sublimation of the crude product gave **244** (mp 125-6°; recrystallized from hexane; lit.[112b,c] mp 126-128°, 128°).

cis-4-Hydroxymethylcyclohexanol (**245**)

A cold (5°) solution of lactone **244** (0.176 g; 1.40 mM) in dry tetrahydrofuran (10 ml) was treated under nitrogen with a tetrahydrofuran solution of lithium aluminum hydride (0.67 *M*; 3.0 ml; 2.01 mM). The mixture was stirred for 10 hr at reflux, hydrolysed with aqueous tetrahydrofuran (5 ml, containing 0.38 ml H_2O), and filtered through Celite. The solid was thoroughly triturated with tetrahydrofuran (4 x 10 ml). The filtrate and washings were combined, concentrated to an oil, taken up in chloroform (10 ml), and dried (anhydr. $MgSO_4$). Removal of solvent gave **245** as a colourless liquid.

ir ($CHCl_3$): 3608 cm^{-1} (m); 3460 (bm); 1019 (m); 978 (m).

nmr ($CDCl_3$): τ 5.97 (bm, 1H); 6.48 (bm, 2H); 8.21 (s, 2H); 8.43 (bm, 9H).

cis-4-Hydroxy-1-cyclohexanemethyl *p*-Toluenesulphonate (**246**)

In preparation for the tosylation reaction, traces of water were removed from **245** by coevaporation (2x) with dry pyridine.

A solution of diol **245** (prepared from 1.4 mM

244) and recrystallized *p*-toluenesulphonyl chloride (0.257 g; 1.35 mM) in dry pyridine (7 ml) was stored at 0° for 24 hr, concentrated (room temperature; 0.02 torr) to *ca*. 0.5 ml, transferred into cold (5°) aqueous hydrochloric acid (7% by wt; 8 ml) and extracted with cold (5°) methylene chloride (3 x 7 ml). The combined extract was washed successively with cold aqueous hydrochloric acid (7%; 3 x 6 ml), water (2 x 6 ml), and aqueous sodium chloride solution (50% saturated; 6 ml) and then dried (anhydr. Na_2SO_4). Removal of solvent and chromatography on silicic acid (21 g; chloroform eluent) afforded the pure monotosylate **246** as a white solid (mp 41.5-43.0°; recrystallized from ether).

Yield: 0.289 g; 73% from **244**.

ir ($CHCl_3$): 3630 cm^{-1} (m); 3600-3250 (bw); 1375 (s), 1193 and 1184 (s).

nmr ($CDCl_3$): τ 2.11-2.85 (m, 4H); 6.12 (m, 3H); 7.55 (s, 3H); 8.32 (s, 1H); 8.47 (bm, 9H).

cis-4-Iodomethylcyclohexanol (**247**)

This experiment was performed by Dr. G. Spessard.

A mixture of monotosylate **246** (0.160 g; 0.563 mM) and anhydrous sodium iodide (0.503 g; 3.36 mM) in dry, purified acetone (3 ml) was refluxed for 20 hr under nitrogen. After cooling, the solvent was removed under reduced pressure. The residue was taken up in chloroform (20 ml), washed with aqueous sodium chloride solution (50% saturated; 10 ml), dried (anhydr. $MgSO_4$), and concentrated to a yellow oil which crystallized upon standing. The crude iodide was sufficiently pure to use for the preparation of 248.

Yield: 74 mg; 59%.

ir (CCl_4): 3610 cm^{-1} (m), 3460 (bm); 967 (s); 912 (s).

nmr ($CDCl_3$): τ 6.03 (bm, 1H); 6.85 (bm, 2H); 7.84 (s, 1H); 8.40 (bm, 9H).

cis-4-Methylcyclohexanol (248)

This experiment was performed by Dr. G. Spessard.

A solution of the hydroxy iodide 247 (70.8 mg; 0.295 mM) and sodium cyanoborohydride (85 mg; 1.3 mM) in dry hexamethylphosphoramide (1.7 ml) was heated at 60-65° for 5 hr and at 70-75° for 14 hr under nitrogen. After cooling, the brown solution was diluted with water (10 ml) and extracted with ether (4 x 10 ml). The combined extract was washed with aqueous sodium chloride solution (50% saturated; 2 x 10 ml), dried (anhydr. $MgSO_4$), and concentrated to give crude 248 as a yellow oil. The nmr spectrum showed little impurity.

Yield: ca. 30 mg; 89%.

ir ($CHCl_3$): 3602 cm^{-1} (m); 3448 (bm); 988 (s).

nmr ($CDCl_3$): τ 6.07 (bm, 1H); 8.07 (s, 1H); 8.56 (bm, 9H); 9.08 (ill-defined doublet, 3H).

5,7-Bis(hydroxymethyl)-2-methylcyclohept-3-en-1-ol (250)

A solution of the lactone 233 (0.992 g; 4.71 mM; recrystallized from cyclohexene) in dry tetrahydrofuran (10 ml), maintained under nitrogen, was treated at 0° with a tetrahydrofuran solution (0.64 M; 25.0 ml; 16.0 mM) of lithium aluminum hydride. After stirring for 20 hr at reflux, the white mixture was cooled to 0°, diluted with dry tetrahydrofuran (15 ml), and hydrolysed by cautiously adding aqueous tetrahydrofuran (13 ml; containing 3.0 g water). The mixture was then stirred at room temperature for 1.5 hr and filtered under vacuum through celite. The collected solid was thoroughly washed with dry tetrahydrofuran (4 x 20 ml). The combined organic solution was stripped of solvent, dissolved in methanolic chloroform (1% by vol; 75 ml), and dried (anhydr. $MgSO_4$-Na_2SO_4; 1:1 by wt). Removal of solvent gave the triol as a colourless glass.

ir (film): 3360 cm^{-1} (bs), 1055 (s); 1027 (s).

2-Methyl-5,7-bis(*p*-toluenesulphonyloxymethyl)cyclohept-3-en-1-ol (**251**)

In preparation for the reaction, trace amounts of water were removed from triol **250** by coevaporation with dry pyridine (2 x 10 ml). A solution of **250** (prepared from 4.71 mM **233**) and *p*-toluenesulphonyl chloride (1.811 g; 9.51 mM) in dry pyridine (12 ml) was stored at 0° for 25 hr. The mixture was concentrated at 20° under reduced pressure to *ca*. 5 ml, poured into cold (5-10°) aqueous hydrochloric acid (7% by wt; 20 ml) and extracted with ether (4 x 15 ml). The combined extract was successively washed with cold (5-10°) aqueous hydrochloric acid (7%, 2 x 15 ml), water (2 x 10 ml), and aqueous sodium chloride solution (50% saturated; 10 ml). The ether was then stripped off and the residue was taken up in methylene chloride (20 ml) and dried (anhydr. Na_2SO_4). After evaporation of the solvent the oily residue was quickly chromatographed on silicic acid (120 g; chloroform--carbon tetrachloride eluent) to give pure **251** as an oil.

Yield: 1.74 g; 75% from **233** (nmr standardization).

ir ($CHCl_3$): 3570 cm^{-1} (bm); 3034 and 3012 (m); 1599 (m); 1360 (s); 1178 and 1190 (s).

nmr ($CDCl_3$): τ 2.10-2.86 (m, 8H); 4.41-4.64 (m, 2H); 5.86-6.39 (m, 3H); 7.30-8.40 (m, 10H); 8.70 (m, 2H); 7.04 (d, J=7 Hz, 3H). τ (aryl $C\underline{H}_3$)

7.55, s. τ (O*H*) 3.83.

mass spectrum: calcd. for $C_{17}H_{22}O_4S$ (251-TsOH); 322.1239.

meas. *m/e*: 322.1245.

2-Methyl-5,7-bis(*p*-toluenesulphonyloxymethyl)cyclohept-3-en-1-yl Benzoate (252)

Compound 251 (0.944 g; 1.91 mM) in dry pyridine (6 ml) at 0° was treated with distilled benzoyl chloride (0.536 g; 3.82 mM). The solution was stored for 24 hr at -5 to 0°, poured into cold (5-10°) aqueous hydrochloric acid (7% by wt; 20 ml), and extracted with benzene--pentane (1:1 by vol; 4 x 15 ml). The combined extract was washed with cold (5-10°) aqueous hydrochloric acid (2 x 15 ml), water (2 x 15 ml), and aqueous sodium chloride solution (50% saturated, 6 ml). The solvents were evaporated and the residue was taken up in methylene chloride (30 ml) and dried (anhydr. Na_2SO_4). Removal of solvent and rapid chromatography of the resulting oil on silicic acid (25 g; chloroform--carbon tetrachloride eluent) furnished the desired benzoate 252 as a colourless oil.

Yield: 1.03 g; ~90% (nmr standardization).

ir (CCl_4): 3070 and 3028 cm^{-1} (m); 1720 (s); 1600 (m); 1292 and 1282 (s).

nmr ($CDCl_3$): τ 2.00-2.92 (m, 13H); 4.39-4.66 (m, 2H); 4.80 (dd, J=2.0, 6.0 Hz, 1H); 6.06 (m, 4H), 6.97-7.92 (m, 9H); 8.45 (m, 2H); 8.99 (d, J=7, 3H). τ (aryl C$\underline{H}_3$): 7.55, s and 7.66 s.

2-Methyl-5,7-bis(iodomethyl)cyclohept-3-en-1-yl Benzoate (255)

To a solution of 252 (0.423 g; 0.706 mM) in dry acetonitrile (3.3 ml) containing some mercury (triply distilled; *ca*. 1.9 g), maintained under nitrogen, was added anhydrous lithium iodide (0.495 g; 3.70 mM). With efficient stirring to disperse the mercury, the reaction mixture was heated to reflux, stirred at reflux for 18 min, and cooled to 0°. The mixture was then decanted from the remaining mercury into aqueous sodium thiosulphate solution (10% by wt; 15 ml) and was extracted with ether (4 x 8 ml). The combined extract was washed with aqueous sodium thiosulphate solution (10%; 2 x 10 ml), water (2 x 10 ml), and saturated aqueous sodium chloride solution (8 ml). The solvent was evaporated and the residue was taken up in methylene chloride (15 ml) and dried (anhydr. Na_2SO_4). Removal of solvent and filtration of the resulting pale yellow oil through silicic acid (20 g; 10% chloroform in carbon tetrachloride eluent) gave the pure diiodide 255 as a pale yellow oil.

Yield: 0.332 g; 92% (nmr standardization).

ir (CCl_4): 1720 cm^{-1} (s); 1271 (s), 1122 (s).

nmr ($CDCl_3$): τ 1.80-2.07 (m, 2H); 2.34-2.83 (m, 3H);

4.30-4.49 (m, 2H); 4.59 (dd, J=2.5, 6.0 Hz, 1H); 6.51-7.83 (m, 7H); 8.12 (m, 2H); 8.89 (d, J=7.4 Hz, 3H).

2,5,7-Trimethylcyclohept-3-en-1-yl Benzoate (258)

The diiodide 255 (0.332 g; 0.650 mM), dissolved in dry dimethoxyethane (1.4 ml) and under nitrogen, was treated with sodium cyanoborohydride (not previously purified; 473 mg; 7.53 mM). (Sodium cyanoborohydride was observed to be extremely hygroscopic.) The brown solution was stirred and dry hexamethylphosphoramide (1.12 ml; 1.15 g; 6.42 mM) was introduced via syringe. After stirring for 38 hr at 75°, the solution was cooled, transferred into water (15 ml), and extracted with ether (3 x 10 ml). The combined extract was concentrated to ca. 1 ml, diluted with benzene--pentane (1:1 by vol; 15 ml), and washed with water (2 x 5 ml) and sodium chloride solution (50% saturated, 5 ml). The organic solution was stripped of solvent and the residue was taken up in methylene chloride (15 ml) and dried (anhydr. Na_2SO_4). Removal of solvent gave the crude product as an oil. Glpc analysis (UCW-98) indicated that 258 composed ca. 75% of the crude product. Three by-products, the benzoate of 260 and two unknown compounds, were present, each with a longer retention time than 258 and each making up ca. 8% of the crude product.

Yield: 0.625 mM of crude mixture; 96% (nmr standardization). *ca.* 0.47 mM as **258**; 72%.

2,5,7-Trimethylcyclohept-3-en-1-ol (**259**)

A solution of crude **258** (*ca.* 52 mg as pure **258**; 0.202 mM) in dry methanol (1.5 ml) was treated with a solution of sodium methoxide in dry methanol (0.840 *M*; 2.50 ml; 2.1 mM). The solution was refluxed under nitrogen for 17 hr, cooled, and poured into dilute aqueous hydrochloric acid (1.0 *M*, 2.1 ml, 2.1 mM). The aqueous layer was saturated with sodium chloride and extracted with methylene chloride (4 x 3 ml). The combined extract was concentrated cautiously at 0° to *ca.* 0.3 ml. After diluting the concentrate with methylene chloride (8 ml) and drying (anhydr. Na_2SO_4), the solvent was again cautiously removed at 0°. Chromatography of the residue on silicic acid (2.5 g; 20% chloroform--carbon tetrachloride eluent) afforded pure **259**. [The composition of chromatography fractions was determined by glpc analysis (UCW-98). Those fractions containing pure **259** were pooled and concentrated by careful spinning-band distillation.]

Yield: 22 mg; 71% (nmr standardization).

ir (CCl_4): 3632 cm^{-1} (w); 3581 (m); 3490 (bm); 3010 (m); 1455 (d, s); 1376 (s); 994 (s).

nmr (100.1 MHz, $CDCl_3$): τ 4.48 (m, 2H); 6.43 (dd, J=

2.0, 6.0 Hz, 1H); 7.41 (bm, 1H); 7.65 (bm, 1H); 7.96 (bm, 1H); 8.16 (bs, 1H); 8.71 (m, 2H); 8.94 (d, J=7.2 Hz, 3H); 8.97 (d, J= 7.2 Hz, 3H); 8.98 (d, J=7 Hz, 3H).

mass spectrum: m/e 154 (P).

2,5,7-Trimethylcyclohept-3-en-1-yl Acetate (261)

Trimethylcycloheptenol 259 (ca. 0.102 g; 0.66 mM) was diluted with dry benzene (2 x 2 ml) and cautiously concentrated at 10°. A solution of 259 and acetic anhydride (0.201 g; 1.97 mM) in dry pyridine (1.5 ml) was heated at 75° under nitrogen for 20 hr. After cooling, the solution was transferred into dilute aqueous hydrochloric acid (7% by wt; 14 ml) and extracted with benzene--pentane (1:1 by vol; 3 x 10 ml). The combined extract was washed successively with dilute aqueous hydrochloric acid (7%; 2 x 10 ml), aqueous sodium bicarbonate solution (50% saturated; 5 ml), water (10 ml), and finally saturated aqueous sodium chloride solution (5 ml). After drying (anhydr. Na_2SO_4), the organic solution was carefully concentrated by spinning-band distillation to ca. 2 ml. The concentrate was then flash-distilled (pot temp 60 to 100°; 0.4 torr) to afford the desired acetate as a colourless liquid. Glpc analysis (Reoplex) showed the product to be at least 95% pure.

Yield: 0.115 g; 89% (nmr standardization).

ir (CCl_4): 3012 cm^{-1} (w); 1735 (s); 1459 (m); 1247 (s).

nmr (CCl_4): τ 4.67 (m, 2H); 5.17 (dd, J=3.1, 6.6 Hz, 1H);
7.15-8.19 (m, 6H); 8.61 (m, 2H); 8.82-9.22
(overlapping doublets, 6H).

mass spectrum: meas. *m/e* 136 ($P-CH_3COOH$).

3-Acetoxy-2,4,6-trimethylheptanedioic Acid (**262**)

A solution of the trimethylheptenyl acetate **261** (0.115 g; 0.590 mM) in *tert*-butanol (40 ml) was introduced into an oxidizing solution (pH 8.5) consisting of aqueous potassium permanganate--sodium periodate solution (0.0975 *M* $NaIO_4$; 0.0025 *M* $KMnO_4$; 70.0 ml; 7.00 mM oxidant), water (140 ml), anhydrous potassium carbonate (1.24 g; 8.97 mM), and *tert*-butanol (110 ml). Stirring at room temperature was initiated. After 50 min reaction, precipitate began to form. After stirring for 20 hr, the red-purple solution was acidified to pH 3.5 with aqueous sulphuric acid (10% by wt). Solid sodium bisulphite was slowly added to reduce the remaining oxidant. During this addition the solution first became colourless, then dark brown and finally yellow. The acidity of the solution was then adjusted to pH 8.0-8.5 with aqueous potassium hydroxide (8.5% by wt; *ca*. 35 ml). The colourless solution was concentrated at 35° under reduced pressure to *ca*. 60

ml. After raising the alkalinity to pH 9-9.5 with aqueous potassium hydroxide solution (8.5% by wt), the now yellowish concentrate was washed with ether (2 x 40 ml), acidified to pH 1.0 with aqueous sulphuric acid (10% by wt), carefully saturated with sodium chloride (sulphur dioxide from excess sodium bisulphite was evolved), and extracted with chloroform (5 x 40 ml). (Subsequent continuous extraction of the aqueous layer with ether afforded only 10 mg of the desired dicarboxylic acid 262.) The combined chloroform extract was concentrated to 20 ml, washed with aqueous sodium chloride solution (50% saturated; 3 x 8 ml), and stripped of solvent. The residue was diluted in methylene chloride (20 ml) and dried (anhydr. Na_2SO_4). Evaporation of solvent gave pure 262 as a crystalline solid (mp 110.1-111.0°; recrystallized from ether--pentane).

Yield: 0.150 g; 98%.

ir ($CHCl_3$): 3600-2400 cm^{-1} (bm); 1735 (m); 1710 (s); 1240-1210 (bm).

nmr (100.1 MHz, $CDCl_3$): τ -2.24 (bs, 2H); 4.86 (dd, J=1.7, 11.0 Hz, 1H); 7.13 (qd, J_q=7 Hz, J_d=11 Hz, 1H); 7.47 (bm, 1H); 7.79-8.69 (m, 5H); 8.76 (d, J=7.0 Hz, 3H); 8.80 (d, J=7.0 Hz, 3H); 9.04 (d, J=6.6 Hz, 3H). The signal for the last proton is probably buried in the absorption at τ 8.60-8.90.

mass spectrum: calcd. mass for $C_{12}H_{20}O_6$: 260.1260.
meas. *m/e*: 260.1255.

analysis: calcd. for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74.
found: C, 55.46; H, 7.61.

5-(1-Carboxyethyl)-2,4-dimethylpentanolide [(±)-**32**]

A solution of **262** (13.5 mg; 0.052 mM) in methanolic sodium methoxide solution (0.5 *M*; 0.75 ml) was refluxed for 3.5 hr, cooled, diluted with water (2.0 ml), and acidified with concentrated hydrochloric acid (3 drops) to pH 1.0. After stirring for 30 min, the solution was saturated with sodium chloride and extracted with ether (4 x 3 ml). The combined ethereal extract was washed with aqueous sodium chloride solution (50% saturated, 2 x 3 ml), concentrated to *ca*. 0.5 ml, diluted with methylene chloride (5 ml), and dried (anhydr. Na_2SO_4). Removal of solvent and chromatography of the resulting oil on silicic acid (1.5 g; 1% methanolic chloroform eluent) gave the pure lactonic acid (±)-**32** as a crystalline solid (mp 112-113°; recrystallized from ether--hexane).

Yield: 8.8 mg; 85% (nmr standardization).

ir ($CHCl_3$): 3600-2400 cm^{-1} (bm); 1725 (s); 1460 (m);

1382 (m); 1189 (m); 1100 (m).

nmr (100.1 Hz, $CDCl_3$): τ 1.30 (bs, 1H); 5.42 (dd, J=2.4, 10 Hz, 1H); 7.26 (qd, J_q=7.1 Hz, J_d=2.4 Hz, 1H); *ca*. 7.51 (m, 1H); 7.86-8.33 (m, 2H); 8.33-8.62 (m, 1H); 8.72 (d, J=6.9 Hz, 3H); 8.81 (d, J=7.2 Hz, 3H); 8.99 (d, J= 6.4 Hz, 3H).

analysis: calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.05.
found: C, 59.56; H, 8.05.

Bicyclo[4.2.1]nona-2,4,7-triene (263)

This experiment was performed by Dr. P. Rossy.

An abbreviated account of the preparation of triene has been reported by Cannell.[120] A more detailed description of reaction conditions is recorded below.

The pyrolysis of norbornadiene dimer was carried out in a flow system consisting of a column (1.0 cm i.d.) packed with glass beads (3 mm diameter; 17 cm height). The temperature was monitored using a chromel-alumel thermocouple, sheathed in stainless steel and inserted directly into the packed bed. A slow, constant flow of nitrogen (*ca*. 20 ml/min) was passed downwards through the bed and through the receiving flask (-78°). The pyrolysis bed was heated to 450 ± 5° and norbornadiene dimer (Aldrich

Chemical Co.; 290 g; 1.73 mole) was introduced, by means of a Hershberg dropping funnel, at a slow, constant rate (1 drop every 5-8 sec; ca. 10 ml every 60-80 min) into the nitrogen stream at the top of the pyrolysis column. (The purity of the triene 263 was greatly affected if the rate of addition of the dimer had not been relatively constant.) The condensed effluent was concentrated (20°, 20 torr) to remove cyclopentadiene and fractionally distilled with a spinning-band apparatus to afford pure 263 (bp 83-84° at 47-48 torr; lit.[120] 81° at 105 torr). The progress of the distillation was followed by glpc (Reoplex).

Yield: 85 g (42%).

nmr (CCl_4): τ 3.68-4.51 (m, 4H); 4.87 (m, 2H); 6.93 (bt, 2H); 8.07 (dt, J_d=11.5 Hz, J_t=6 Hz, 1H); 8.70 (d, J=11.5 Hz, 1H).

exo-Bicyclo[4.2.1]nona-2,4-dien-7-ol (274)

The procedure outlined by Brown and coworkers[146] was followed for the preparation of di(isoamyl)borane. Thus a solution of 2-methyl-2-butene (15.79 g; 225 mM) in dry tetrahydrofuran (30 ml) was added dropwise over ca. 20 min to a stirred, cold (5°) solution of borane in tetrahydrofuran (1.03 M; 108 ml; 111 mM), maintained under a nitrogen atmosphere. The solution of dialkylborane was stirred for 3 hr at 5° and then was added dropwise, over 35 min, to a cold (0-5°), stirred solution of bicyclo-[4.2.1]nona-2,4,7-triene (263; 12.90 g; 109 mM) in dry tetrahydrofuran (35 ml). The solution was stirred for 2 hr at 0-5° and for 20 hr at room temperature. The reaction mixture was cooled to 0-5° and hydrolysed by first adding aqueous sodium hydroxide solution (3.0 *M*; 43 ml; 129 mM) in several portions and then aqueous hydrogen peroxide (9.05 *M*; 38 ml; 343 mM). The hydrogen peroxide was added at such a rate as to maintain the temperature of the reaction mixture between 30-40°. The resulting cloudy mixture was vigorously stirred for 2.0 hr at room temperature and then extracted with ether (2 x 75 ml). The combined extract was washed with water (75 ml) and saturated aqueous sodium chloride solution (75 ml), concentrated to *ca*. 30 ml, diluted with methylene chloride (200 ml), and dried (anhydr. Na_2SO_4). Evaporation of the solvent left an oil which was fractionally distilled to give 274 as a low-melting crystalline solid (bp 78-81° at 0.3 torr). Glpc analysis (Reoplex, 180°) indicated 274 to be *ca*. 90% pure.

Yield: 10.4 g; 90% pure; 63% as 274.

ir (CCl_4): 3626 cm^{-1} (m); 3348 (bm); 3025 (m); 1597 (w); 1029 (s).

nmr (100 MHz, CCl_4): τ 3.75-4.65 (m, 4H); 5.78 (m, 1H);

7.21 (m, 1H); 7.38-8.78 (m, 7H).

τ ($\underline{H}$-C_9) 8.38 (d, J=11.6 Hz, 1H).

τ ($\underline{HO}$-C_7) 7.53 (s).

Bicyclo[4.2.1]nona-2,4-dien-7-one (**275**)

Aluminum *tert*-butoxide was prepared by the procedure reported in "Organic Syntheses".[147] Commercial *p*-quinone was purified either by sublimation or by recrystallization from Skelly B. The procedure for Oppenauer oxidation outlined by Wiberg *et al*.[148a] and by Bly and Bly[148b] was adopted with certain modifications.

To a solution of the *exo*-alcohol **274** (95% purity; 3.22 g; 22.5 mM as **274**) and *p*-quinone (10.4 g; 96.3 mM) in dry ether (200 ml), maintained under nitrogen, was added a solution of aluminum *tert*-butoxide (5.93 g; 24.1 mM) in dry ether (100 ml). When heated to reflux, the solution quickly developed a deep purple colour and a precipitate. After 40 hr reflux, the mixture was cooled to room temperature and carefully washed with aqueous hydrochloric acid (3*M*, 6 x 100 ml), aqueous sodium hydroxide solution (5% by wt; 5 x 100 ml), and aqueous sodium chloride solution (50% saturated; 3 x 100 ml). The ether was removed (5° at 20 torr) and the residue was taken up in methylene chloride and dried (anhydr. Na_2SO_4). Evaporation of the solvent at 5° and flash distillation of the resulting yellow oil gave the desired ketone 275 (bp *ca.* 60° at 0.5 torr). Glpc analysis (Reoplex) of the distilled ketone indicated the presence of some starting alcohol (274, *ca.* 10%). Filtration through silicic acid (47 g; methylene chloride--pentane eluent) provided 275 free of 274 and of *ca.* 98% purity (glpc analysis). (Whenever 275 was to be ultimately converted to the *cis* dicarboxylic acid 214, it was not necessary to remove the small amount of 274.)

Yield: 2.34 g; 98% purity; 80%.

ir (CCl_4): 3034 cm^{-1} (m); 1743 (s); 1596 (m).

nmr (100.1 MHz, CCl_4): τ 3.67-4.62 (m, 4H); 6.73 (m, 1H); 7.09 (m, 1H); 7.41-8.00 (m, 3H); 8.23 (tdd, J_d=12.5, 3.2 Hz, J_t=1.6 Hz, 1H).

mass spectrum: calcd. mass for $C_9H_{10}O$: 134.0732.
meas. *m/e*: 134.0728.

8-Hydroxymethylenebicyclo[4.2.1]nona-2,4-dien-7-one (278)

This experiment was performed by Dr. G. Spessard.

A procedure similar to that described by Ainsworth[149] was used. Ethyl formate was dried by distilling from phosphorus pentoxide.

A solution of 275 (88% purity; 7.29 g; 47.8 mM as 275) and dry ethyl formate (6.50 ml; 5.92 g; 80.0 mM) in dry ether (50 ml) was added dropwise over 20 min to a cold (0-5°), stirred suspension of sodium hydride (56% dispersion in mineral oil; 3.0 g; 70 mM) and ethanol (98%; 0.5 ml; 8.3 mM) in dry ether (200 ml), maintained under nitrogen. The mixture was stirred at room temperature for 21 hr and then treated with ethanol (98%; 2.5 ml). After an additional 1 hr stirring, the mixture was treated with water (50 ml). After approximately 5 min, two homogeneous layers formed. The mixture was further diluted with water (50 ml). The organic layer was decanted and extracted with water (2 x 100 ml). The combined aqueous solution was washed with ether (2 x 50 ml), cooled (0-5°), mixed with methylene chloride (50 ml), and finally acidified to pH 1-2 with aqueous hydrochloric acid (10% by wt). The methylene chloride layer was decanted and the aqueous solution was extracted with methylene chloride (3 x 100 ml). The combined methylene chloride solution was dried (anhydr. Na_2SO_4) and stripped of solvent to give crude 278 as a pink solid (mp 112-115°). The product was of sufficient purity for direct use in the periodate cleavage reaction.

Yield: 7.5~~8~~ g; 98%.

ir ($CHCl_3$): 3600-2500 cm^{-1} (bm); 1673 (s); 1600 (s).

nmr (CCl_4): τ -1.07 (bs, 1H); 2.73 (s, 1H); 3.50-4.41 (m, 4H); 6.60 (bt, 2H); 7.35-7.87 (m, 1H); 8.26 (d, J=11.6 Hz, 1H).

cis-4,6-Cycloheptadiene-1,3-dicarboxylic Acid (214) from 278

This experiment was performed by Dr. Spessard following the method described by Cornforth, Cornforth, and Popjak[125] with important modifications.

A solution of sodium periodate (30.3 g; 142 mM) in water (200 ml) was added rapidly to a cold (0-5°), stirred solution of the crude hydroxymethylene ketone 278 (7.54 g; *ca.* 46.5 mM) in dioxane (100 ml), under a nitrogen atmosphere. After complete addition of the periodate solution, the cold reaction mixture was further diluted with water (200 ml). Stirring and cooling was maintained for 1.0 hr during which aqueous sodium hydroxide solution (10% by wt; *ca.* 34 ml) was gradually added to hold the pH of the reaction mixture at 4.5-5.0. (After approximately 30 min, no further addition of base was required.) The mixture was stirred 4.5 hr at room temperature and then filtered through Celite. The collected precipitate was washed with dioxane (100 ml). The combined filtrate and washings was concentrated (25° at 15 torr) to 400 ml, acidified to pH

1-2 with aqueous hydrochloric acid (10% by wt), extracted with ether (1 x 150 ml), saturated with sodium chloride, and again extracted with ether (4 x 150 ml). Washing the combined extract with saturated sodium chloride solution (100 ml) followed by drying (anhydr. $MgSO_4$) and evaporation of solvent afforded 214 of excellent purity, as a tan, granular solid. (The nmr spectrum of the dimethyl ester of this product contained no signals attributable to the *trans* isomer.)
Yield: 8.16 g; 96%.

endo-Bicyclo[4.2.1]nona-2,4-dien-7-ol (279)

A solution of ketone 275 (freed of 274; 2.15 g; 16.0 mM) in ether (25 ml), maintained under nitrogen, was cooled to -78° and treated with an ethereal solution of lithium aluminum hydride (1.64 *M*; 5.5 ml; 9.0 mM). The mixture was stirred for 15 min at 0°, diluted with ether (75 ml), and hydrolysed by the successive addition of water (0.33 ml), aqueous sodium hydroxide (15% by wt; 0.33 ml), and water (1.00 ml). After work-up in the usual manner, the crude product was diluted in methylene chloride, dried (anhydr. Na_2SO_4), stripped of solvent, and flash distilled. Compound 279 was obtained as a white crystalline solid (mp 36.5-37.2°; recrystallized from pentane).

Yield: 1.96 g; 90%.

ir (CCl_4): 3630 cm^{-1} (w); 3582 (m); 3440 (s); 1080 (s).

nmr (100.1 MHz, CCl_4): τ 3.80-4.60 (m, 4H); 5.73 (dt, J_d=8.7 Hz, J_t=6.5 Hz, 1H), 7.18 (bq, J≈6, 1H); 7.47 (bq, 1H); 7.64-8.57 (m, 5H).

endo-Bicyclo[4.2.1]nona-2,4-dien-7-yl Acetate (285)

A mixture of the *endo* alcohol 279 (0.304 g; 2.24 mM), acetic anhydride (0.457 g; 4.48 mM), and pyridine (3.0 ml) was stirred at 70° for 6.0 hr. After the usual work-up, the product was flash distilled to afford pure 285 as a colourless oil.

Yield: 0.394 g; 99%.

ir (CCl_4): 3128 cm^{-1} (m); 1737 (s); 1249 (s).

nmr (CCl_4): τ 4.26 (bm, 4H); 5.02 (cq, J≈9 Hz, 1H); 6.79-8.49 (m, 9H). τ ($C\underline{H}_3CO$) 8.04 (s).

endo-Bicyclo[4.2.1]nonan-7-ol (283)

After a vigorously stirred suspension of platinum oxide (9.9 mg) in methanol (1.0 ml) had been reduced by hydrogen (1 atm; room temperature), a solution of 285 (40.0 mg; 0.224 mM) in methanol (1.5 ml) was introduced.

The mixture was stirred for 2.5 hr, filtered, and stripped of solvent. The residue was taken up in methylene chloride, dried (anhydr. Na_2SO_4), and reconcentrated. Glpc analysis (UCW-98, Carbowax 20m) indicated that **286** was homogeneous. The saturated acetate **286**, dissolved in dry methanol (1.5 ml), was treated with a catalytic amount of sodium methoxide (*ca*. 5 mg; 0.9 mM), heated at reflux for 15 min, cooled, and transferred into water (5 ml). Extraction of the product with ether and drying in the usual manner (methylene chloride and anhydr. Na_2SO_4) gave pure **283** as a crystalline solid.

Yield: *ca*. 28 mg; 90%.

ir (CCl_4): 3630 cm^{-1} (m); 3460 (m).

nmr (CCl_4): τ 5.80 (dt, $J_d \approx 9$ Hz, $J_t \approx 7$ Hz, 1H); 7.50-9.10 (m, 15H).

Preparation of Diols **291** and **292** from *endo* Alcohol **279**

A solution of *endo* alcohol **279** (0.154 g; 1.13 mM) and *m*-chloroperbenzoic acid (82% pure; 0.250 g; 1.19 mM) in methylene chloride (5 ml) was stirred at 0° for 5.0 hr. Enough methanol was added to dissolve the precipitated *m*-chlorobenzoic acid and the solution was then esterified with an excess of ethereal diazomethane. After removal of solvents and excess diazomethane, the crude allylic epoxides were taken up in methylene chloride, dried (anhydr. Na_2SO_4), and again freed of solvent.

Approximately two-thirds of the product (*i.e.* from 0.75 mM **279**) was dissolved in dry tetrahydrofuran (5 ml), treated at 0° under nitrogen with a tetrahydrofuran solution of lithium aluminum hydride (1.9 *M*; 1.6 ml; 3.0 mM), and stirred overnight at room temperature. The reaction mixture was hydrolysed and the product was isolated in the usual manner. Analysis by glpc (Carbowax 20m) showed the product to consist of mainly three compounds, *m*-chlorophenylmethanol, **291**, and **292**. Chromatography of the mixture on silicic acid (2x; 4.5 g and 2.0 g; 1% methanol in chloroform eluent) afforded a sample of diol **291** (90% pure; *ca*. 18 mg). (The total amount of diols **291** and **292** isolated after chromatography was *ca*. 98 mg, equivalent to a yield of 85%.)

Spectral data of **291**

nmr (100.1 MHz, $CDCl_3$): τ 4.26 (m, 2H); 5.70 (dt, J_d=8.7 Hz, J_t=6.6 Hz, 1H); 6.04 (dt, J_d=5.5 Hz, J_t=3.5 Hz, 1H); 7.19 (bq, 1H); 7.30-7.90 (m, 7H); 8.31-8.90 (m, 2H).

ir ($CHCl_3$): 3614 cm^{-1} (m); 3548 (sh); 3454 (bm); 3014 (m).

The spectral data for diol 292 are reported in the following experiment.

Bicyclo[4.2.1]non-4-ene-2,8-diol (292)

A solution of pure diacetate 308 (mp 56.2-57.2°; 16.0 mg; 0.0678 mM) in dry methanol (1.5 ml), containing a small amount of sodium methoxide (*ca*. 4.0 mg) was heated at reflux for 15 min. The solution, maintained under nitrogen, was cooled to -78° and neutralized (pH 6.5) with a stream of carbon dioxide. After warming to room temperature the solvent was removed under reduced pressure (20 torr) and the residue was diluted in methylene chloride (2 ml) and dried (anhydr. Na_2SO_4). Evaporation of the solvent and flash distillation gave pure 292 as a colourless oil.

Yield: *ca*. 10.0 mg; 100%.

ir ($CHCl_3$): 3604 cm^{-1} (m); 3426 (bm).

nmr (100.0 MHz, $CDCl_3$): τ 4.05 (m, 1H); 4.50 (m, 1H); 5.60 (dt, J_d=8.8 Hz, J_t=6.6 Hz, 1H); 5.81 (bq, 1H); 7.22-8.10 (m, 8H); 8.42-8.76 (m, 2H).

Oxidation of Diol 292

A solution of crude 292 (*ca*. 75% pure, contamininated with 15% 291 and 10% unknown diol products; 5.9 mg; 0.038 mM as diols) in acetone (distilled from potassium permanganate; 1.5 ml) at 0° was treated with Jones' reagent (20 μl; 0.053 mMCrO$_3$), prepared by the method of C. Djerassi and coworkers.[150] The mixture was stirred for 5.5 min, the reaction was quenched by adding two drops of methanol, and after an additional 0.5 min stirring the mixture was poured into a solution of sodium bicarbonate (11.0 mg) in water (3.0 ml). The aqueous solution was extracted with methylene chloride (4x4 ml). The combined extract was washed with water (4 ml) and concentrated to a small amount of oil. The product was taken up in methylene chloride, dried (anhydr. Na$_2$SO$_4$), and again stripped of solvent.

Yield: *ca.* 5.4 mg.

ir (CCl$_4$): 3620 and 3484 cm^{-1} (w); 3028 (w); 1745 (s); 1707 (s).

uv (cyclohexane): λ_{max} < 210 nm (end absorption); 299 nm ($\varepsilon \approx 20$).

The saturated diols 306 and 310 were first prepared from impure samples of 291 and 292. When the pure crystalline diacetates 304 and 308 became available, the syntheses of 306 and 310 were repeated starting from these pure intermediates. These latter experiments are described below.

Bicyclo[4.2.1]nonane-2,7-diyl Diacetate (305)

A vigorously stirred suspension of platinum oxide (16 mg) in ethyl acetate (1.5 ml) was reduced by hydrogen (1 atm; room temperature). To the mixture was then added a solution of diacetate 304 (pure; 96.9 mg; 0.405 mM) in ethyl acetate (1.5 ml). After stirring for 6.5 hr, the mixture was filtered and the filtrate was concentrated to a colourless oil. Glpc (UCW-98) showed 305 to be pure.

Yield: 97 mg; 100%.

ir (CCl_4): 1736 cm^{-1} (s); 1263 and 1241 (s); 1100-1020 (s).

nmr (100.1 MHz, CCl_4): τ 5.03 (dt, J_d=10.4 Hz, J_t=7.2 Hz, 1H); 5.28 (bt, 1H); 7.26-8.90 (m, 18H). τ ($C\underline{H}_3COO$) 7.99 (s) and 8.03 (s).

Bicyclo[4.2.1]nonane-2,7-diol (306)

The transesterification of 305 was performed as described above for the preparation of pure 292. Thus from the treatment of 305 (50.0 mg; 0.208 mM) with hot methanol containing a catalytic amount of sodium methoxide, the desired diol (306) was isolated as an oil.

Yield: 31.0 mg; 95%.

ir ($CHCl_3$): 3603 cm^{-1} (m); 3445 (m); 1261 (m); 1060 (m).

nmr (100.1 MHz, $CDCl_3$): τ 5.71 (dt, J_d=9.8 Hz, J_t=7.1 Hz, 1H); 6.22 (bt, 1H); 7.40-8.90 (m, 14H).

Bicyclo[4.2.1]nonane-2,7-dione (**307**)

A cold (0°) solution of **306** (prepared from 90% pure **291**; 17 mg; 0.11 mM) in acetone (distilled from potassium permanganate; 1.5 ml) was treated with Jones' reagent[150] (59 μl; 0.157 mM CrO_3) and stirred for 6.0 min. After quenching the reaction with a few drops of methanol, the mixture was poured into water (7 ml), which was then extracted with methylene chloride (4x4 ml). The combined extract was washed with aqueous sodium bicarbonate solution (50% saturated; 6 ml) and saturated sodium chloride solution and was then dried (anhydr. Na_2SO_4). Evaporation of the solvent and flash distillation of the residue produced the diketone **308** as a crystalline solid. The product was homogeneous on glpc (UCW-98; Carbowax 20m).

Yield: 14 mg; 84%.

ir (CCl_4): 1743 cm^{-1} (s); 1703 cm^{-1} (s).

nmr (100.1 MHz, CCl_4): τ 6.92 (m, 1H); 7.20-8.00 (m, 8H); 8.00-8.60 (m, 3H).

In the preparation of 1,3-diketone **311** from **292**, the experimental procedures employed were analogous to those used to prepare **307**. For brevity, only the results of the experiments are summarized below.

Bicyclo[4.2.1]nonane-2,8-diyl Diacetate (**309**)

Hydrogenation of pure **292** (103.2 mg; 0.434 mM) gave **309**, homogeneous by glpc (UCW-98), as a colourless oil.

Yield: 100.4 mg; 96%.

ir (CCl_4): 1738 cm^{-1} (as doublet, s); 1368 (m); 1244 (s).

nmr (100.1 MHz, CCl_4): τ 4.96 (m, 2H); 7.63 (m, 3H); 7.96 (s, 3H); 8.06 (s, 3H); 8.10-9.00 (m, 9H).

Bicyclo[4.2.1]nonane-2,8-diol (**310**)

Treatment of pure diacetate **309** (43.2 mg; 0.180 mM) with hot methanol containing a small quantity of sodium methoxide led smoothly to diol **310**.

Yield: 26.5 mg; 94%.

ir ($CHCl_3$): 3610 cm^{-1} (m); 3430 (bm); 1265 (m); 1070 (m).

nmr ($CDCl_3$): τ 5.36-5.94 (m, 2H); 7.18 (s, 2H); 7.34-9.22 (m, 12H).

Bicyclo[4.2.1]nonane-2,8-dione (**311**)

The sample of diol **310** was prepared from impure

292 (*ca*. 70% pure, contaminated with 20% **291** and 10% unknown diols). The crude mixture of diols **310** and **306** (25 mg; 0.16 mM) in acetone was oxidized with Jones' reagent (103 µl; 0.275 mM CrO_3). The diketones were isolated as an oil. Glpc analysis (UCW-98) indicated the presence of mainly two compounds. The smaller glpc peak exhibited retention times identical with those of **307** (prepared from **306**) on two systems (UCW-98; Carbowax 20m).

Yield: *ca*. 21 mg; 86%.

ir (CCl_4): 1746 cm^{-1} (s); 1702 (s).

Epoxidation of *endo* Acetate **285** and the Purification of Diacetates **304** and **308**

The epoxidation of the *endo* acetate **285** with *m*-chloroperbenzoic acid and the subsequent reduction of the allylic epoxides with lithium aluminum hydride was executed in the manner employed previously for the conversion of the *endo* alcohol **279** into the diols **291** and **292**. Thus a methylene chloride solution of acetate **285** (0.383 g; 2.15 mM) was epoxidized with *m*-chloroperbenzoic acid (82% pure; 0.467 g; 2.22 mM) and the esterified (diazomethane) products were reduced with a tetrahydrofuran solution of lithium aluminum hydride (1.30 *M*; 6.0 ml; 7.8 mM). By glpc (Carbowax 20m) it appeared that the two diols **291** and 292 were formed in about the same proportion (*ca*. 60:40) as observed in the experiments with 279. The crude product was filtered through silicic acid (8.0 g; 1% methanol in chloroform eluent) to remove the *m*-chlorophenylmethanol and then was acetylated (acetic anhydride and pyridine; 70° for 6.0 hr). Glpc (Reoplex) indicated that besides the two expected diacetates, a third compound (presumably also a diacetate) constituted about 15% of the mixture. The two major diacetates were separated as crystalline substances by preparative glpc (Reoplex). Each was recrystallized twice from pentane. The physical data for the pure compounds are summarized below.

Diacetate 304

mp 76.3-77.2°

ir (CCl_4): 3034 cm^{-1} (w); 1735 (s); 1370 (m); 1240 (s).

nmr (100.1 MHz, CCl_4): τ 4.47 (m, 2H); 5.11 (m, 2H);
7.01 (m, 1H); 7.30-8.90 (m, 13H).

mass spectrum: calcd. for $C_{13}H_{18}O_4$: 238.1205.
meas. *m/e*: 238.1209.

analysis: calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61.
found: C, 65.39; H, 7.48.

Diacetate 308

mp 56.2-57.2°

ir (CCl_4): 3030 cm^{-1} (w); 1739 (s).

nmr (100.1 MHz, CCl_4): τ 4.03 (m, 1H); 4.61 (m, 1H); 4.91 (m, 2H); 7.14-7.75 (m, 5H); 7.75-8.16 (m, 7H); 8.27-8.70 (m, 2H).

mass spectrum: calcd. for $C_{13}H_{18}O_4$: 238.1205.
meas. *m/e*: 238.1209.

analysis: calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61.
found: C, 65.74; H, 7.40.

n-Butyl OO-Hydrogen Monoperoxyphthalate (316)

The procedure of Ogata and Sawaki[132] was modified to make it more suitable for the preparation of 313. The effect of the modifications was examined on the yield for conversion of 315 to 316. The synthesis of 316 was carried out in the presence of cyclododecene to determine whether any epoxidation occurs during the addition of the acyl chloride to the excess of hydroperoxide. (Epoxidation under such conditions could arise if the mixing of the two solutions was not efficient.)

To a cold (5°) mixture of aqueous sodium hydroxide (6.9 *M*; 1.96 ml; 13.5 mM), magnesium sulphate (14 mg), and water (1.0 ml) was added aqueous hydrogen peroxide (9.4 *M*; 1.44 ml; 13.5 mM) and finally purified dioxane (2.5 ml). A solution of 315 [prepared from 0.517 g (2.32 mM) *n*-butyl hydrogen phthalate (**314**) and oxalyl chloride] and cyclododecene (mixture of isomers; 0.412 g; 2.48 mM) in purified dioxane (2.5 ml) was then slowly introduced over 3-4 min into the vigorously stirred, cold (4-7°) hydroperoxide solution. The mixture was stirred for an additional 10 min, and diluted with water (10 ml) and the cyclododecene was extracted with ether (3 x 10 ml). [The combined extract was washed with water until the washings tested at pH 6.0, and was dried (anhydr. Na_2SO_4). The solvent was evaporated and the residue was examined by glpc. At most 2% cyclododecene epoxides were present.] The diluted hydroperoxide solution was then added dropwise into a cold (5°), vigorously stirred mixture of ether (10 ml) and aqueous sulphuric acid (1.92 *M*; 10 ml). After addition was complete, the mixture was immediately neutralized to pH 3.0-3.5 with dilute aqueous sodium bicarbonate solution. The mixture was extracted with chloroform (4 x 20 ml) and the combined extract was washed with water (30 ml) and dried (anhydr. Na_2SO_4). Quantitative analysis for peracid and residual hydrogen peroxide using standard methods (see for instance reference 132) indicated that **316** was formed in 70% yield. (Without modification of the experimental procedure of Ogata and Sawaki, the yield of **316** was 84%.)

endo-Bicyclo[4.2.1]nona-2,4-diene-7-yl Hydrogen Phthalate (317)

The procedure cited in reference 151 was modified somewhat for this experiment.

A solution of endo alcohol 279 (0.349 g; 2.56 mM), phthalic anhydride (sublimed; 0.419 g; 2.83 mM), and pyridine (0.480 mM; 6.08 mM) in dry benzene (2.5 ml) was stirred at 70° for 14 hr, cooled, and transferred into cold (5°) aqueous hydrochloric acid (7% by wt; 10 ml). The mixture was extracted with chloroform (3 x 10 ml) and the combined extract was washed with aqueous hydrochloric acid (15 ml) and then water (15 ml). Evaporation of the chloroform left a colourless oil which was dissolved in an aqueous sodium carbonate solution (0.380 g Na_2CO_3, 3.58 mM; 20 ml water) and washed with ether (2 x 20 ml). The aqueous solution was then acidified with dilute hydrochloric acid to pH 1.0 and extracted with chloroform (3x 20 ml). The combined chloroform extract was washed with water (2x20 ml), concentrated to a white solid, dissolved in methylene chloride (20 ml), and dried (anhydr. Na_2SO_4). Evaporation of the solvent and recrystallization of the solid residue from ether--hexane afforded pure 317 (mp 118.0-119.5°).

Yield: 0.700 g; 96%.

ir ($CHCl_3$): 3600-2400 cm^{-1} (bm); 1720-1700 (bs); 1301 and 1288 (s).

nmr ($CDCl_3$): τ -1.89 (s); 2.00-2.56 (m, 4H); 3.70-4.86 (m, 5H); 6.84 (m, 1H); 7.04-8.30 (m, 5H).

mass spectrum: calcd. mass for $C_{17}H_{16}O_4$: 284.1049.
found m/e: 284.1045.

Bicyclo[4.2.1]nonan-8-ol-2-yl p-Toluenesulphonate (321)

A solution of 310 [prepared from pure 308; dried by azeotropic distillation using dry pyridine (2x4 ml); 26.5 mg; 0.17 mM] and p-toluenesulphonyl chloride (36.2 mg; 0.185 mM) in dry pyridine (1.0 ml) was stored at 0° for 30 hr. The solution was diluted with cold chloroform (5 ml), transferred into cold (5°) aqueous hydrochloric acid (7% by wt; 8 ml), and extracted with chloroform (5 ml). The aqueous layer was saturated with sodium chloride and again extracted with chloroform (4x5 ml). The combined organic extract was concentrated to 4 ml and was washed with cold aqueous hydrochloric acid (7% by wt; saturated with sodium chloride; 3 ml), cold aqueous sodium bicarbonate solution (50% saturated; 3 ml), and finally cold saturated sodium chloride solution (3 ml). After drying (anhydr. Na_2SO_4), the solvent was evaporated. Chromatography of the residue on silicic acid (2.0 g;

chloroform eluent) afforded **321** (>90% pure by nmr).

Yield: *ca.* 20.2 mg; 34%.

ir ($CHCl_3$): 3600-3150 cm^{-1} (bm); 1600 (m); 1191 and 1179 (s).

nmr (100.0 MHz, $CDCl_3$): τ 2.22 (m, 2H); 2.70 (m, 2H); 5.00 (m, 1H); 5.66 (dt, $J_d \simeq 9$ Hz, $J_t \simeq 7$-8 Hz, 1H); 7.42-8.00 (m, 6H); 8.0-9.1 (m, 10H).

Bicyclo[4.2.1]nonane-2,8-diyl Carbonate (**323**)

A solution of hydroxy tosylate **321** (15 mg; 0.048 mM) and tetrabutylammonium hydrogen carbonate (prepared by accident from the air oxidation of the corresponding formate; 103 mg; 0.34 mM) in purified, dry acetone (4.0 ml) was stirred under nitrogen for 2 hr at room temperature. The solution was concentrated to 1 ml at reduced pressure and room temperature, transferred into water (4.0 ml), and extracted with methylene chloride (4x5.0 ml). The combined extract was concentrated to an oil, diluted in benzene (4.0 ml), washed with dilute aqueous sodium bicarbonate (pH 8.5; 2x3.0 ml), dried (anhydr. Na_2SO_4), and stripped of solvent. The residue was chromatographed on silicic acid (0.75 g; 30-50% chloroform in carbon tetrachloride eluent). Compound **323** was obtained as a crystalline solid, homogenous on glpc (UCW-98).

Yield: ca. 8.0 mg; 93%.

ir ($CHCl_3$): 1738 cm^{-1} (s); 1396 (s).

nmr (100.1 MHz, $CDCl_3$): τ 5.03 (m, 1H); 5.41 (dt, $J_d \approx 10$ Hz, $J_t \approx 5$-6 Hz, 1H); 7.16 dq, $J_q \approx$ 8.4 Hz, $J_d \approx 1.5$ Hz, 1H); 7.30-9.00 (m, 13H).

mass spectrum (chemical ionization): (i) CH_4; m/e 183 (P+1).
(ii) NH_3; m/e 200 (P+18).

endo,endo-Bicyclo[4.2.1]nonane-2,8-diol (**320**)

The carbonate **323** (6.0 mg; 0.033 mM) was treated with dry methanol which contained a small amount of sodium methoxide. The solution was refluxed for 25 min and then diluted with water (1.0 ml) and acidified to pH 1.5 with concentrated hydrochloric acid. (Some gas was evolved during the acidification process--presumably carbon dioxide.) The solution was concentrated to ca. 1 ml at room temperature and reduced pressure, transferred into water (2.0 ml), saturated with sodium chloride, and extracted with methylene chloride (4x3 ml). The combined extract was washed with saturated sodium chloride solution and dried (anhydr. Na_2SO_4). Removal of solvent and sublimation of the product gave **320** as an oil.

Yield: 4.3 mg; 83%.

ir ($CHCl_3$): 3625 and 3600 cm^{-1} (w); 3500 (bm); 1016 (m).

nmr (100.1 MHz, $CDCl_3$): τ 5.52 (dt, J_d=10 Hz, J_t=7 Hz, 1H);
6.30 (m, 1H); 6.66 (bs, 2H);
7.15-8.80 (m, 12H).

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